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Original Investigation

Estimated GFR and Incident Cardiovascular Disease Events in American Indians: The Strong Heart Study

Nawar M. Shara, PhD,[1,2,3] Hong Wang, MD,[1,2] Mihriye Mete, PhD,[1,2] Yaman Rai Al-Balha, MD,[1,4] Nameer Azalddin, MD,[1,5] Elisa T. Lee, PhD,[6] Nora Franceschini, MD,[7] Stacey E. Jolly, MD,[8] Barbara V. Howard, PhD,[1,2,3] and Jason G. Umans, MD, PhD[1,2,3]

Background: In populations with high prevalences of diabetes and obesity, estimating glomerular filtration rate (GFR) by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation may predict cardiovascular disease (CVD) risk better than by using the Modification of Diet in Renal Disease (MDRD) Study equation.

Study Design: Longitudinal cohort study comparing the association of GFR estimated using either the CKD-EPI or MDRD Study equation with incident CVD outcomes.

Setting & Participants: American Indians participating in the Strong Heart Study, a longitudinal population-based cohort with high prevalences of diabetes, CVD, and CKD.

Predictor: Estimated GFR (eGFR) predicted using the CKD-EPI and MDRD Study equations.

Outcomes: Fatal and nonfatal cardiovascular events, consisting of coronary heart disease, stroke, and heart failure.

Measurements: The association between eGFR and outcomes was explored in Cox proportional hazards models adjusted for traditional risk factors and albuminuria; the net reclassification index and integrated discrimination improvement were determined for the CKD-EPI versus MDRD Study equations.

Results: In 4,549 participants, diabetes was present in 45%; CVD, in 7%; and stages 3-5 CKD, in 10%. During a median of 15 years, there were 1,280 cases of incident CVD, 929 cases of incident coronary heart disease, 305 cases of incident stroke, and 381 cases of incident heart failure. Reduced eGFR ($<$90 mL/min/1.73 m^2) was associated with adverse events in most models. Compared with the MDRD Study equation, the CKD-EPI equation correctly reclassified 17.0% of 2,151 participants without incident CVD to a lower risk (higher eGFR) category and 1.3% ($n = 28$) were reclassified incorrectly to a higher risk (lower eGFR) category.

Limitations: Single measurements of eGFR and albuminuria at study visits.

Conclusions: Although eGFR based on either equation had similar associations with incident CVD, coronary heart disease, stroke, and heart failure events, in those not having events, reclassification of participants to eGFR categories was superior using the CKD-EPI equation compared with the MDRD Study equation.

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INDEX WORDS: Cardiovascular disease risk; chronic kidney disease; estimated glomerular filtration rate; Strong Heart Study.

Early identification of chronic kidney disease (CKD) may lead to better targeting of prevention efforts, allocation of health care resources, and patient outcomes. Decreased estimated glomerular filtration rate (eGFR), creatinine clearance, or the presence of micro- or macroalbuminuria each predict cardiovascular disease (CVD).[1,2] Each of these measures of CKD also has been shown to predict incident CVD in American Indians, a population with a high prevalence of obesity, diabetes mellitus, and incident CVD events.[1] In the absence of measured GFR, we often depend on serum creatinine (SCr)-based eGFR to assess kidney function, particularly in population-based studies. However, our previous work showed that adding albuminuria to SCr-based eGFR may help identify individuals at higher risk of coronary heart disease (CHD).[3] Since then, the CKD Epidemiology Collaboration (CKD-EPI) developed an equation, also

From the [1]MedStar Health Research Institute, Hyattsville, MD; [2]Georgetown-Howard Universities Center for Clinical and Translational Science; [3]Georgetown University, Washington, DC; [4]School of Medicine, Damascus University, Damascus, Syria; [5]All Saints University School of Medicine, Commonwealth of Dominica; [6]College of Public Health, University of Oklahoma, Oklahoma City, OK; [7]Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC; and [8]Cleveland Clinic Medicine Institute, Cleveland, OH.

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Address correspondence to Nawar M. Shara, PhD, MedStar Health Research Institute, 6525 Belcrest Rd, Ste 700, Hyattsville, MD 20782. E-mail: nawar.shara@medstar.net

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based on SCr measures, to improve GFR estimation.[4] Several studies have suggested that the CKD-EPI equation serves as a better risk predictor than the Modification of Diet in Renal Disease (MDRD) Study equation in some populations and improves overall risk reclassification compared with the MDRD Study equation.[5-8] A recent study showed similar results with all-cause mortality, CVD, and end-stage renal disease mortality as outcomes.[9] Thus, the CKD-EPI equation may improve CVD risk prediction compared with estimates based on the MDRD Study equation. In this article, we use SCr values from the Strong Heart Study (SHS) phase 1 examination (1989-1991) that were recalibrated to an isotope-dilution mass spectrometry (IDMS)-traceable SCr assay to estimate GFR using the IDMS-traceable 4-variable MDRD Study equation and the CKD-EPI equation. Our aim was to examine the performance of the 2 equations in predicting CVD, CHD, heart failure (HF), and stroke in this American Indian population with a high baseline prevalence of obesity, diabetes, and CKD.

METHODS

Study Population and Variables

Data from the SHS, a population-based longitudinal study of CVD risk in American Indians aged 45-74 years, were used for the present analysis. The SHS was initiated in 1988 to investigate CVD and its risk factors in geographically diverse groups of American Indians. The Indian Health Service, institutional review boards, participating tribes, and the MedStar Health Research Institute approved the study. All participants provided informed consent. The SHS design, survey methods, and laboratory techniques have been published.[10] The SHS cohort of 4,549 includes men and women who were seen at the first (1989-1991), second (1993-1995), and third (1998-2000) examinations.

Of 4,549 SHS participants, those missing SCr values (n = 173) and/or having prevalent CVD (n = 331) at the baseline examination were excluded. Those with SHS IDMS-calibrated SCr level <0 mg/dL (n = 1) and extreme eGFR values calculated by using the IDMS-traceable 4-variable MDRD Study equation (>2,000 mL/min/1.73 m^2; n = 3) also were excluded, leaving 4,081 participants (40% men) for the present analysis. Criteria used to define definite fatal myocardial infarction, stroke, CHD, and nonfatal CVD have been published, as have methods for ascertaining incident CVD events.[10-12] Of 4,081 participants, 1,280 (31%) developed incident CVD during a median 15-year follow-up.

Baseline Examination and Laboratory Measures

Baseline and follow-up examinations consisted of a personal interview and physical examination. Baseline demographic information, medical history, and smoking status were collected during the interview. Height, weight, waist and hip circumferences, systolic blood pressure, and diastolic blood pressure were measured using standardized protocols by trained personnel. Fasting blood samples were obtained for measurement of lipids, insulin, SCr, fibrinogen, and glycated hemoglobin. Urine samples were collected to measure albumin and creatinine. Detailed clinical and laboratory measures have been published.[10,13]

Hypertension was defined as the use of antihypertensive medication, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg. Micro- and macroalbuminuria were defined as urinary albumin-creatinine ratio of 30-299 mg/g and ≥300 mg/g, respectively. Diabetes was identified by use of hypoglycemic agents, fasting glucose level ≥126 mg/dL, or self-report of diagnosis by a physician.[14]

Serum Creatinine Recalibration

During SHS phase 1, SCr was measured using an alkaline picrate rate method (Roche Diagnostics, www.rocheusa.com/portal/usa/indianapolis) on the Hitachi 717 platform.[10,11] For the present analyses, we randomly selected 300 stored serum specimens from SHS phase 1, including 60 from each quintile of the SCr distribution. We then added all 39 available samples with baseline values of 2.2-4.8 mg/dL because these were under-represented in the original sample of 300. All samples were thawed, centrifuged, and assayed in triplicate using an IDMS-traceable slide-based enzymatic creatinine assay on the Vitros Fusion 5,1 platform (Ortho Clinical Diagnostics, www.orthoclinical.com/en-us/Pages/Home.aspx). Original and IDMS-traceable SCr values and their paired differences (IDMS-traceable SCr minus original SCr) were compared using scatterplots (Fig S1, available as online supplementary material), Bland-Altman plots (Fig S2), and Deming regression.[15] Finally, the derived calibration equation (SHS IDMS-calibrated SCr = −0.159 + [0.980 × original SHS SCr]) was assessed by residual analysis. This calibration equation was similar to that reported previously for NHANES (National Health and Nutrition Examination Survey) samples collected and assayed in 1988-1994 (−0.184 + [0.96 × original NHANES SCr]).[16]

Estimation of GFR

As described in the previous section, we recalibrated SCr to IDMS-traceable values. Then we estimated GFR by the IDMS-traceable 4-variable MDRD Study equation[17] as $eGFR_{MDRD} = 175 \times (\text{standardized SCr})^{-1.154} \times \text{Age}^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$, where SCr is measured in milligrams per deciliter, and age, in years. In addition, we estimated GFR by the CKD-EPI equation[4] as $eGFR_{CKD\text{-}EPI} = 141 \times (\text{minimum of standardized SCr [mg/dL]}/\kappa \text{ or } 1)^{\alpha} \times (\text{maximum of standardized SCr [mg/dL]}/\kappa \text{ or } 1)^{-1.209} \times 0.993^{\text{age}} \times (1.018 \text{ if female}) \times (1.159 \text{ if black})$, where κ is 0.7 if female and 0.9 if male and α is −0.329 if female and −0.411 if male. Because the SHS includes only American Indians, the equation factors for race were dropped for all participants for both equations. Previous researchers have handled American Indian data similarly or used a constant midway between those for whites and blacks.[18]

In a supplemental analysis, eGFR was calculated using the original 4-variable MDRD Study equation[19] ($eGFR = 186 \times (\text{uncalibrated SCr})^{-1.154} \times \text{Age}^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$, where SCr is measured in milligrams per deciliter and age is measured in years) and the original SHS SCr values. We also compared eGFR values calculated with this original 4-variable MDRD Study equation and the CKD-EPI equation (Table S1).

eGFR originally was categorized using the cutoff values suggested by NKF-KDOQI (National Kidney Foundation's Kidney Disease Outcomes Quality Initiative): >90, 60-89, 30-59, 15-29, and <15 mL/min/1.73 m^2.[20] Because of the small number of participants with eGFR <15 mL/min/1.73 m^2 (n = 17), participants in this category were combined with those having eGFR of 15-29 mL/min/1.73 m^2. Further, we separated high eGFR (≥120 mL/min/1.73 m^2) values into a separate category because of the possibility that these may reflect loss of muscle mass, diabetic hyperfiltration, or inaccurately estimated GFR values.[21] Therefore, our results are presented in the following categories: ≥120, 90-<120, 60-<90, 30-<60, and <30 mL/min/1.73 m^2.