Risk of Incident ESRD: A Comprehensive Look at Cardiovascular Risk Factors and 17 Years of Follow-up in the Atherosclerosis Risk in Communities (ARIC) Study

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Background: Diabetes and hypertension are potent risk factors for end-stage renal disease (ESRD). Previous studies suggest that other cardiovascular risk factors also may increase the risk of ESRD; however, risk associated with a comprehensive cardiovascular risk-factor assessment has not been quantified in a population-based sample.

Study Design: The Atherosclerosis Risk in Communities (ARIC) Study, a prospective observational cohort.

Setting & Participants: 15,324 white and African American participants aged 45-64 years from 4 US communities were followed up after a baseline visit that occurred in 1987-1989.

Predictor: A comprehensive collection of cardiovascular risk factors were examined.

Outcomes & Measurements: Incidence of ESRD (transplant, dialysis, catheter placement or kidney failure, and death) exclusive of acute kidney failure was ascertained through active surveillance of hospitalizations through 2004.

Results: During a median 16-year follow-up, 241 cases of ESRD developed (incidence rate, 1.04 cases/1,000 person-years). Male sex, African American race, diabetes, hypertension, history of coronary heart disease, smoking, older age, body mass index, and triglyceride concentration were associated with increased risk of ESRD after adjustment for baseline estimated glomerular filtration rate (eGFR) and each other. There was a graded curvilinear association between risk of ESRD and lower baseline eGFR at levels < 90 mL/min/1.73 m^2 and moderately increased levels > 120 mL/min/1.73 m^2. The relative risk of eGFR on ESRD risk generally was greater in women and individuals with diabetes than in their counterparts.

Limitations: Only events occurring in acute-care hospitals were investigated (but there was long-term continuous active surveillance of events).

Conclusions: We quantify the relative risk of ESRD in a community-based African American and white population associated with established cardiovascular risk factors (diabetes, hypertension, male sex, and African American race) and report prospective data identifying greater risk of ESRD associated with other cardiovascular risk factors: moderately decreased eGFR, increased eGFR, higher body mass index, smoking, and increased triglyceride level.

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INDEX WORDS: End-stage renal disease; renal failure; estimated glomerular filtration rate; glomerular filtration rate.

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End-stage renal disease (ESRD) poses a substantial health burden to afflicted individuals and a substantial cost burden to the US health care system. The risk of death is $>$ 4-fold higher in persons with ESRD compared with the general population.[1] The estimated total Medicare costs of ESRD in 2006 reached $22.7 billion.[2]

The incidence of ESRD in the United States has increased substantially during the last decade, from 258 per million in 1995 to 363 per million in 2006.[2] The increased incidence may

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be caused in part by an increased prevalence of diabetes and hypertension, 2 potent cardiovascular risk factors for ESRD.[3-5] More than 71% of incident ESRD cases in the United States are attributed to diabetes or hypertension.[2]

Cardiovascular disease shares several other risk factors with chronic kidney disease and kidney dysfunction.[6-12] Other cardiovascular risk factors also may be shared with ESRD, but have not yet been well quantified. The relationship of lipid levels with ESRD risk is uncertain and best studied using standardized measurements in fasting participants.

The relationship between severely decreased estimated glomerular filtration rate (eGFR) and risk of ESRD is well established.[13-15] However, the relationship between risk of ESRD at moderately decreased eGFRs has not been well studied. Understanding the continuous and complex relationship between eGFR and incident ESRD is critical and needs to be evaluated in a large study using standardized measures of serum creatinine (SCr).

Despite the burden, cost, and increasing incidence of ESRD, few other risk factors for ESRD have been identified. Because of the relatively low incidence, few prospective community-based studies have the sample size and length of follow-up required to study incident ESRD. Prospective administrative data identify age, minority racial and ethnic groups,[2] and history of cardiovascular disease as risk factors for ESRD.[4,16] Similar factors have been found in health care plan data,[17,18] which also have identified increased body mass index (BMI)[19,20] (or obesity status[21]) and increased fasting plasma glucose,[22] hemoglobin, and uric acid levels and nocturia[21] as risk factors for ESRD. However, these studies are subject to selection bias and may not be generalizable to the general population. Additional biases may be present because of the use of clinically indicated, rather than systematic and standardized, measurements. Prospective data from the general population are especially limited, with the notable exception of the Second National Health and Nutrition Examination Survey (NHANES II) follow-up data, which provided a rigorous analysis, but included only 44 incident ESRD cases.[23]

In this study, we comprehensively investigated cardiovascular risk factors that also may be risk factors for ESRD. We studied a general population sample using the Atherosclerosis Risk in Communities (ARIC) Study cohort of African American and white middle-aged adults followed for up to 17 years.

METHODS

Study Population

The ARIC Study is a prospective observational cohort of 15,792 self-reported African American and white individuals between the ages of 45 and 64 years from 4 US communities (Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, MD). Participants took part in examinations starting with a baseline visit (visit 1) between 1987 and 1989. Individuals had 3 follow-up examinations at ~3-year intervals at community clinics, as well as annual follow-up telephone interviews. Hospitalized events were ascertained continuously from enrollment through December 31, 2004. Details of the ARIC Study have been published elsewhere.[24]

Participants who were missing baseline SCr values (n = 375), were missing both low-(LDL) and high-density lipoprotein (HDL) cholesterol values (n = 111), reported a race other than white or African American (n = 48), and African Americans from the Minnesota and Washington County study centers (n = 54) were excluded (the latter 2 exclusions were due to small numbers, because participant demographics were inconsistent with planned center and race sampling schemes). Analyses are based on the remaining 15,324 study participants who were followed up from the baseline visit until the earliest date of incident ESRD, death, or December 31, 2004.

Data Collection

Demographic (including self-reported race and sex) and health behavior data, medical history, and measurements of height, weight, and blood pressure were obtained during each clinical examination. Blood was drawn at all clinic visits, as described previously.[25] Diabetes mellitus was defined as fasting glucose level ≥ 126 mg/dL, nonfasting glucose level ≥ 200 mg/dL, self-reported physician diagnosis of diabetes mellitus, or use of oral hypoglycemic medication or insulin.

Three seated blood pressure measurements were performed by certified technicians using a random-zero sphygmomanometer after 5 minutes of rest. The mean of the second and third readings was recorded. Enzymatic methods were used to obtain total plasma cholesterol, HDL cholesterol, and triglyceride levels, whereas LDL cholesterol was calculated from these using the Friedewald equation.[26] Participants with incalculable LDL cholesterol concentration because of a triglyceride concentration ≥ 400 mg/dL (n = 138) were assigned the study population mean LDL cholesterol value (137 mg/dL). Smoking status was determined by self-reported cigarette smoking. Prevalent coronary heart disease (CHD) was defined as a history of physician-