AJKD
Original Investigation

# Measures of Kidney Disease and the Risk of Venous Thromboembolism in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study

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**Background:** Kidney disease has been associated with venous thromboembolism (VTE) risk, but results conflict and there is little information regarding blacks.

**Study Design:** Prospective cohort study.

**Setting & Participants:** 30,239 black and white adults 45 years or older enrolled in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study 2003 to 2007.

**Predictors:** Estimated glomerular filtration rate (eGFR) using the combined creatinine–cystatin C ($eGFR_{cr\text{-}cys}$) equation and urinary albumin-creatinine ratio (ACR).

**Outcomes:** The primary outcome was adjudicated VTE, and secondary outcomes were provoked and unprovoked VTE, separately. Mortality was a competing-risk event.

**Results:** During 4.6 years of follow-up, 239 incident VTE events occurred over 124,624 person-years. Cause-specific HRs of VTE were calculated using proportional hazards regression adjusted for age, sex, race, region of residence, and body mass index. Adjusted VTE HRs for $eGFR_{cr\text{-}cys}$ of 60 to <90, 45 to <60, and <45 versus ≥90 mL/min/1.73 $m^2$ were 1.28 (95% CI, 0.94-1.76), 1.30 (95% CI, 0.77-2.18), and 2.13 (95% CI, 1.21-3.76). Adjusted VTE HRs for ACR of 10 to <30, 30 to <300, and ≥300 versus <10 mg/g were 1.14 (95% CI, 0.84-1.56), 1.15 (95% CI, 0.79-1.69), and 0.64 (95% CI, 0.25-1.62). Associations were similar for provoked and unprovoked VTE.

**Limitations:** Single measurement of eGFR and ACR may have led to misclassification. Smaller numbers of events may have limited power.

**Conclusions:** There was an independent association of low eGFR (<45 vs ≥90 mL/min/1.73 $m^2$) with VTE risk, but no association of ACR and VTE.

*Am J Kidney Dis.* 70(2):182-190. 

***INDEX WORDS:*** Chronic kidney disease (CKD); kidney disease measures; venous thromboembolism (VTE); deep vein thrombosis and pulmonary embolus; race; glomerular filtration rate (GFR); albumin-creatinine ratio (ACR); albuminuria; renal insufficiency; vascular disease.

Chronic kidney disease (CKD) affects 13% of the general population[1] and is a strong independent risk factor for death and cardiovascular disease (CVD), including stroke, coronary disease, heart failure, and peripheral arterial disease.[2] There is an increased risk for venous thromboembolism (VTE) in patients with nephrotic syndrome,[3] patients receiving maintenance dialysis,[4] and kidney transplant recipients,[5,6] but the risk for VTE in patients with earlier stages of CKD is unclear.[7-9] VTE comprises deep vein thrombosis and pulmonary embolism and is the third leading vascular disease in the United States, affecting approximately 500,000 Americans each year and contributing to more than 100,000 deaths annually.[10] Prior studies linking measures of kidney function and VTE conflict, possibly due to varying composition and limited statistical power or the use of different kidney disease measures in these studies, including various equations for estimated glomerular filtration rate (eGFR) and definitions of albuminuria.

To better elucidate the relationship between CKD and VTE, we assessed the associations of kidney disease measures with incident VTE in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study. We had 4 primary aims. First, we sought to determine the association of albuminuria and

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*Received June 2, 2016. Accepted in revised form October 30, 2016. Originally published online January 23, 2017.*

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*0272-6386*
*http://dx.doi.org/10.1053/j.ajkd.2016.10.039*

eGFR, in particular eGFR based on combining creatinine and cystatin C levels ($eGFR_{cr\text{-}cys}$), and VTE in the REGARDS Study. Second, because results of prior studies disagreed as to whether CKD is more strongly associated with unprovoked or provoked VTE[9,11] (which refers to VTE that followed major trauma, surgery, or marked immobility or associated with active cancer or chemotherapy within 90 days), we evaluated associations of kidney disease measures with each VTE type. We hypothesized that the association would be larger for provoked than unprovoked VTE because persons with CKD might be more likely to be hospitalized and require surgery. Third, because prior studies had limited numbers of black participants and CKD disproportionately affects blacks, we sought to evaluate whether race modified the association of CKD and VTE. Finally, to contextualize the importance of CKD with regard to VTE risk, we compared the population-attributable fraction for a range of kidney function to that of older age and obesity, which are established VTE risk factors.

## METHODS

### Study Population and Design

We studied participants in the REGARDS Study, a prospective nationally representative cohort study of blacks and whites in the United States, which has been previously described.[12] The REGARDS Study enrolled 30,239 black and white men and women 45 years or older in 2003 to 2007. Due to the goals of REGARDS to assess black-white disparities in stroke and cognitive decline, only self-identified non-Hispanic white and black individuals were included. Additional exclusion criteria included medical conditions preventing long-term participation, active cancer, active treatment for cancer, residence in or awaiting placement in a nursing home, or inability to communicate in English. For this analysis, we excluded participants who had baseline VTE, were missing measures of kidney disease, or who reported being on dialysis therapy.

Participants were identified from commercially available lists of residents and recruited through a mailing followed by telephone contact (response rate, 33%). Of eligible participants contacted, the cooperation rate was 49%, which is similar to that of many other cohort studies. Participants first completed a computer-assisted telephone interview for self-reported demographic, risk factor, and medications data. Then they underwent an in-home visit, at which written informed consent was obtained and anthropomorphic data, medication inventory, and urine samples were collected and fasting phlebotomy were performed. During the in-home examination, standardized protocols were followed to obtain 2 blood pressure measurements that were averaged for analysis, an electrocardiogram, height, and weight. Blood and urine samples were collected after a 10- to 12-hour fast. Blood was centrifuged locally and shipped with urine samples on ice packs to the University of Vermont Laboratory for Clinical and Biochemistry Research for reprocessing and analysis or storage.[13] The study was approved by all institutional review boards at participating universities, including the University of Alabama (IRB 00000726), and University of Vermont (CHRMS 00-295).

### Laboratory Methods

Serum creatinine was measured using an isotope-dilution mass spectrometry–traceable method[14] using the Vitros 950IRC instrument (Johnson & Johnson Clinical Diagnostics), with a coefficient of variation (CV) of 1.1%. Urinary albumin was measured with the BN ProSpec nephelometer (Dade Behring) with CVs of 2.2% at 110 mg/L and 4.3% at 13 mg/L. Urinary creatinine was measured with a rate-blanked Jaffé procedure, using the Modular-P analyzer (Roche/Hitachi) with CVs of 2.6% at 66 mg/dL and 8.6% at 156 mg/dL. Serum cystatin C was measured with high-sensitivity particle-enhanced immunonephelometry (N Latex Cystatin C on the BNII; Dade Behring), with an intra-assay CV of 2.0% to 2.8% and interassay CV of 2.3% to 3.1%.

### Definitions

eGFR was calculated using the CKD-EPI (CKD Epidemiology Collaboration) equations based on creatinine ($eGFR_{cr}$), cystatin C ($eGFR_{cys}$), and combined creatinine and cystatin C levels ($eGFR_{cr\text{-}cys}$).[15] eGFR was categorized as $<45$, 45 to $<60$, 60 to $<90$, and $\geq 90$ mL/min/1.73 $m^2$ to correspond to clinical categories. Urinary albumin-creatinine ratio (ACR) was categorized as $<10$, 10 to $<30$, 30 to $<300$, and $\geq 300$ mg/g.

Covariates of interest were obtained at baseline and included age, sex, race (self-reported as black or white), region of residence (southeast or nonsoutheast), body mass index (BMI) in kilograms per meter squared, hypertension, diabetes, hyperlipidemia, CVD, smoking, self-report of current postmenopausal hormone therapy, and aspirin, statin, or warfarin use. Hypertension was defined as systolic blood pressure $>$ 140 mm Hg and/or diastolic blood pressure $>$ 90 mm Hg and/or use of antihypertensive medication. Diabetes was defined as fasting glucose level $>$ 126 mg/dL, nonfasting glucose level $>$ 200 mg/dL, or use of diabetes medication. Hyperlipidemia was defined as cholesterol level $>$ 240 mg/dL or low-density lipoprotein cholesterol level $>$ 160 mg/dL or taking medications for high cholesterol level. CVD was defined as self-report of prebaseline myocardial infarction, aortic aneurysm, stent, coronary artery surgery, or stroke.

### Identification and Validation of Outcomes

The primary outcome was incident VTE, ascertained as previously described.[16] In brief, medical records were obtained from potential VTE events, each of which was reviewed by 2 physicians, and major disagreements were settled by a blinded third reviewer.[16] Provoked VTE was defined as a VTE that was preceded within 90 days by major trauma, surgery, or marked immobility or associated with active cancer or chemotherapy. All other events were considered unprovoked. The competing event of death was identified through active surveillance, including calls to participants and search of online sources (eg, Social Security Death Index and National Death Index). Further details of ascertainment were previously reported.[17,18]

### Statistical Analysis

We compared baseline characteristics among participants across $eGFR_{cr\text{-}cys}$ and ACR categories using analysis of variance for continuous variables and $\chi^2$ tests for categorical variables. Dichotomous variables were expressed as percentage, and continuous variables, as mean $\pm$ standard deviation.

We calculated age-, sex-, and race-adjusted incidence rates of VTE per 1,000 person-years with 95% confidence intervals (CIs) for each kidney disease measure using Poisson regression. We used Cox proportional hazards regression to estimate cause-specific hazard ratios (HRs) with 95% CIs for the competing risk of VTE and mortality. Observation time was defined as time from completing the baseline in-home visit to time of loss to follow-up, end of follow-up, or event. Participants were censored for death in the VTE model and censored for VTE for the mortality model.[19] To control for confounding, we created a multivariable model including demographics (age, sex, race, and region of residence) and established VTE risk factors (BMI) to adjust