Published in final edited form as:

Am J Kidney Dis. 2017 August ; 70(2): 182–190. doi:10.1053/j.ajkd.2016.10.039.

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

Katharine L. Cheung, MD, MSc, FRCPC,

Larner College of Medicine, University of Vermont

Neil A. Zakai, MD, MSc,

Larner College of Medicine, University of Vermont

Aaron R. Folsom, MD, MPH,

University of Minnesota

Manjula Kurella Tamura, MD, MPH,

Stanford University and VA Palo Alto Health Care System, Geriatrics Research Education and Clinical Center

Carmen A. Peralta, MD, MAS,

University of California San Francisco

Suzanne E. Judd, MPH, PhD,

University of Alabama- Birmingham

Peter W. Callas, PhD, and

Corresponding author: Katharine L Cheung, MD, MSc, FRCPC, Division of Nephrology, 2309 UHC Med-Nephrology, 1 South Prospect Street, University of Vermont, Burlington, VT, 05401, tel: 802-847-2534; fax: 802-847-8736 klcheung@med.uvm.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

This work was presented in abstract and poster form at the American Heart Association Epidemiology and Prevention | Lifestyle and Cardiometabolic Health conference in March 2015.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

Contributions: Research idea and study design: KLC, MC, NAZ, MKT, ARF; data acquisition: SEJ, NAZ, MC; data analysis/interpretation: KLC, NAZ, PWC, MC, MKT, ARF, CAP; statistical analysis: KLC, PWC; mentorship: NAZ, MC. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. KLC takes responsibility that this study has been reported honestly, accurately and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Peer Review: Evaluated by 2 peer reviewers, a Statistical Editor, a Co-Editor, and Editor-in-Chief Levey.

Supplementary Material

Table S1: Age-, sex-, and race-adjusted incidence rates and HRs of VTE for categories of eAER.

Table S2: Adjusted cause-specific HRs for VTE and mortality by ACR stratified by race and region.

Table S3: Incidence rates and HRs of VTE for eGFR equations.

Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

Supplementary Material Descriptive Text for Online Delivery

Supplementary Table S1 (PDF). Age-, sex-, and race-adjusted incidence rates and HRs of VTE for categories of eAER.

Supplementary Table S2 (PDF). Adjusted cause-specific HRs for VTE and mortality by ACR stratified by race and region.

Supplementary Table S3 (PDF). Incidence rates and HRs of VTE for eGFR equations.

University of Vermont

Mary Cushman, MD, MSc

Larner College of Medicine, University of Vermont

Abstract

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 aged 45 years or older enrolled in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study 2003–2007.

Predictors—Estimated glomerular filtration rate (eGFR) using the combined creatinine-cystatin C (eGFR_{cr-cysC}) 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—Over 4.6 years' 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. The adjusted VTE HRs for eGFR_{cr-cysC} 60–<90, 45–<60 and <45 versus ≥90 ml/min/1.73m² 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). The adjusted VTE HRs for ACR 10–<30, 30–<300, ≥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 m²) with VTE risk, but no association of ACR and VTE.

Keywords

chronic kidney disease (CKD); kidney disease measures; venous thromboembolism; deep vein thrombosis and pulmonary embolus; race; glomerular filtration rate (GFR); albumin-creatinine ratio (ACR); renal insufficiency

Chronic kidney disease (CKD) affects 13% of the general population¹ and is a strong independent risk factor for death and cardiovascular disease including stroke, coronary disease, heart failure and peripheral arterial disease.² There is an increased risk of venous thromboembolism (VTE) in nephrotic syndrome,³ in patients receiving maintenance dialysis,⁴ and in kidney transplant recipients^{5, 6} but the risk of VTE in patients with earlier stages of CKD is unclear.^{7–9} Venous thromboembolism 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 measures of

kidney disease 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 four primary aims. First, we sought to determine the association of albuminuria and eGFR, in particular eGFR based on combining creatinine and cystatin C (eGFR_{Cr-CysC}), 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, since 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 regards 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 aged 45 years or older in 2003–2007. 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.

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, urine samples 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 the 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 (CHRS 00-295).

Laboratory Methods

Serum creatinine was measured using an isotope-dilution mass spectrometry–traceable method¹⁴ using the Vitros 950IRC instrument (Johnson & Johnson Clinical Diagnostics, Rochester, NY), with a coefficient of variation (CV) of 1.1%. Urinary albumin was measured with the BN ProSpec nephelometer (Dade Behring, Marburg, Germany) with a CV of 2.2% at 110 mg/L and of 4.3% at 13 mg/L. Urinary creatinine was measured with a rate-blanked Jaffé procedure, using the Modular-P analyzer (Roche/Hitachi) with a CV of 2.6% at 66 mg/dL and of 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, Deerfield, IL), with an intra-assay CV of 2.0%–2.8% and an inter-assay CV of 2.3%–3.1%.

Definitions

The eGFR was calculated using the CKD-EPI equations based on creatinine (eGFR_{Cr}), cystatin C (eGFR_{CysC}) and combined creatinine–cystatin C (eGFR_{Cr-CysC}).¹⁵ The eGFR was categorized as <45, 45–<60, 60–<90, and ≥90 ml/min/1.73m² to correspond to clinical categories. Urinary albumin-creatinine ratio (ACR) was categorized as <10, 10–<30, 30–<300, ≥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 non-southeast), body mass index (BMI) in kg/m², hypertension, diabetes, hyperlipidemia, cardiovascular disease (CVD), smoking, self-report of current postmenopausal hormone therapy (HT), aspirin (ASA), statin or warfarin use. Hypertension is defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or use of antihypertensive medication. Diabetes is defined as fasting glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, or use of diabetes medication. Hyperlipidemia was defined as cholesterol ≥240 mg/dL or low-density lipoprotein cholesterol ≥160 mg/dL or taking medications for high cholesterol. Cardiovascular disease was defined as a self-report of pre-baseline 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 two physicians and major disagreements 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 (e.g. Social Security Death Index, National Death Index). Further details of ascertainment were previously reported.^{17, 18}

Statistical Analysis

We compared baseline characteristics among participants across eGFR_{Cr-CysC} and ACR categories using ANOVA for continuous variables and χ^2 tests for categorical variables. Dichotomous variables were expressed as percentages and continuous variables as means $\pm$ standard deviation.

We calculated age-, sex- and race-adjusted incidence rates of VTE per 1000 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. The observation time was defined as time from completing the baseline in-home visit to time of lost 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, region of residence) and established VTE risk factors (BMI) to adjust associations of kidney disease measures and VTE. An interaction of race $\times$ region for VTE risk was previously reported in REGARDS, so this interaction term was included in the model.¹⁶ The same covariates were used to estimate adjusted HRs for provoked and unprovoked VTE. Mortality models were additionally adjusted for hypertension, diabetes, hyperlipidemia, history of CVD and smoking. Violations of the Cox proportional hazards model assumptions were assessed by visual inspection of the log-minus-log survival plots and by testing global and individual Schoenfeld residuals. We tested for interactions among kidney disease measures and race (black/white), adjusting for age, sex and BMI, and stratified by region to account for known interaction between race and region. We also tested for an interaction between eGFR and ACR.

In a secondary analysis, we estimated the HRs and 95% CIs for VTE using eGFR_{Cr}, eGFR_{CysC} using the CKD-EPI (CKD Epidemiology Collaboration) equation and eGFR_{Cr} using the MDRD (Modification of Diet in Renal Disease) Study equation to understand whether a difference in estimating equations could account for conflicting reports in the association of kidney disease measures and VTE.

We calculated the population attributable fraction of CKD (using a range of eGFR_{Cr-CysC} cut points: <45, <60 and <90 ml/min/1.73 m²), age (≥ 65 versus <65 years) and obesity (BMI ≥ 30 versus <30 kg/m²) for VTE using the punafcc command in Stata. To reconcile our null findings with the literature showing an association of albuminuria and VTE, we performed a post-hoc sensitivity analysis using estimated albumin excretion rate (eAER), which is the product of ACR and estimated creatinine excretion rate, using Ix's formula.²⁰

$$\text{eAER} = \text{ACR} * [879.89 + (12.51 * \text{weight in kg}) - (6.19 * \text{Age}) + (34.51 \text{ if black}) - (379.42 \text{ if female})]$$

Statistical significance was considered as a two-tailed $P < 0.05$, and, for interaction analyses, as $p < 0.10$. All statistical analyses were performed using Stata software version 14 (StataCorp LP).

Results

The initial cohort included 30,239 participants. After exclusions for missing baseline home visit or follow-up data (n=684), self-report of dialysis (n=113), or baseline VTE (n=1,749), there were 27,749 participants. A total of 2,601 participants (8.6% of initial cohort) were missing any kidney disease measure with the following nonmutually exclusive counts: serum creatinine (n=1,871), serum cystatin C (n=2,518), urine albumin (2,002) and urine creatinine (n=1,929). The final analysis included 25,102 participants (Figure 1).

The analytic cohort was 54% female, 40% black, and 48% age 65 years or older. There were 9% with $\text{eGFR}_{\text{Cr-CysC}} < 60 \text{ ml/min/1.73m}^2$, 11% with $\text{eGFR}_{\text{Cr}} < 60 \text{ ml/min/1.73m}^2$, 15% with $\text{eGFR}_{\text{CysC}} < 60 \text{ ml/min/1.73m}^2$ and 14% with $\text{ACR} \geq 30 \text{ mg/g}$. There were 50 participants with $\text{ACR} > 3000 \text{ mg/g}$ and only one VTE occurred in this subcategory.

Compared to those with higher $\text{eGFR}_{\text{Cr-CysC}}$ at baseline, participants with lower $\text{eGFR}_{\text{Cr-CysC}}$ were older; more likely to have hypertension, diabetes, or hyperlipidemia; more likely to be a former or never smoker; and more likely to use statins, aspirin or warfarin (Table 1). For higher compared to lower ACR categories, diabetes, hypertension, CVD, and current smoking were more common (Table 2).

There were 239 VTE events (113 unprovoked, 126 provoked) during 124,624 person-years' follow-up. The incidence rates of VTE with 95% CIs are shown in Table 3 and increased monotonically across categories of declining $\text{eGFR}_{\text{Cr-CysC}}$. The incidence rates of VTE increased across categories of ACR, except for the highest category ($\geq 300 \text{ mg/g}$), where the number of events was limited. The incidence rates of mortality increased across declining eGFR and higher ACR categories.

The risk of VTE increased with declining $\text{eGFR}_{\text{Cr-CysC}}$ (Table 4); the unadjusted HRs for $\text{eGFR}_{\text{Cr-CysC}}$ 60–<90, 45–<60 and <45 compared to $\geq 90 \text{ ml/min/1.73m}^2$ were 1.91 (95% CI, 1.45–2.51), 2.24 (95% CI, 1.41–3.57) and 3.38 (95% CI, 2.04–5.60), respectively (p for trend <0.001). The HRs were attenuated when adjusting for age, sex, race $\times$ region and BMI and remained statistically significant only for $\text{eGFR}_{\text{Cr-CysC}} < 45$ compared to $\geq 90 \text{ ml/min/1.73m}^2$ (HR, 2.13; 95% CI, 1.19–3.76). Associations of $\text{eGFR}_{\text{Cr-CysC}}$ with provoked and unprovoked VTE were similar, with a two-fold increased risk for each type of VTE with $\text{eGFR}_{\text{Cr-CysC}} < 45$ versus $\geq 90 \text{ ml/min/1.73m}^2$ (Table 4).

In the competing risk analysis, the adjusted cause-specific HRs for mortality increased with lower $\text{eGFR}_{\text{Cr-CysC}}$ and were higher than the HRs for VTE in each category of eGFR (Table 4).

ACR was not associated with VTE in univariate or multivariable analysis. As compared to $\text{ACR} < 10 \text{ mg/g}$, the unadjusted HRs for VTE for $\text{ACR} 10\text{--}<30$, $30\text{--}<300$ and $\geq 300 \text{ mg/g}$ were 1.30 (95% CI, 0.96–1.76), 1.54 (95% CI, 1.06–2.22), and 1.18 (95% CI, 0.52–2.66), respectively. Multivariable HRs are shown in Table 4. The HRs were similar for provoked and unprovoked VTE (Table 4), and for use of the eAER (Table S1, provided as online supplementary material). The adjusted cause-specific HRs for mortality increased across higher levels of albuminuria (Table 4).

Race-specific HRs for VTE by kidney disease measures were stratified by region given the known race $\times$ region interaction in REGARDS (Table 5). For whites residing outside of the southeast, VTE risk increased across categories of eGFR_{Cr-CysC} (HR for eGFR_{Cr-CysC} <45 ml/min/1.73 m², 3.37; 95% CI, 1.34–8.45). For blacks residing outside of the southeast, eGFR_{Cr-CysC} was not associated with VTE, however the P for interaction value for race $\times$ GFR was 0.7 outside the southeast. In the southeast, associations appeared larger in blacks than whites (p for interaction = 0.1), with similar associations in blacks and whites for eGFR <45 ml/min/1.73 m² (HRs of 1.68 and 1.95, respectively) but higher HRs among blacks than whites for eGFR 45–<90 ml/min/1.73m². There were no significant differences in the association of ACR with VTE when stratified by race and region (p for interaction was 0.9 in southeast and 0.3 in non-southeast) (Table S2). There was also no significant interaction between ACR and eGFR (p for interaction = 0.4).

The population attributable fractions of obesity (defined as BMI $\geq$ 30 kg/m²) and older age (defined as age $\geq$ 65 years) for VTE were 17% and 36%, respectively. The population attributable fractions of CKD for VTE by eGFR_{Cr-CysC} <90 and <60 ml/min/1.73 m² and by eGFR_{Cr-CysC} <45 ml/min/1.73m² were 20%, 5% and 4%, respectively.

In a secondary analysis, the eGFR using alternate equations had similar associations with VTE (Table S3). The adjusted HRs for eGFR <45 compared to $\geq$ 90 ml/min/1.73m² were 1.93 (95% CI, 1.13–3.32) for eGFR_{Cr} and 1.58 (95% CI, 0.81–3.08) for eGFR_{CysC}. The HR for VTE with eGFR_{Cr} <45 ml/min/1.73m² using the MDRD Study equation was 1.94 (95% CI, 1.07–3.50).

Discussion

Estimated glomerular filtration rate was independently associated with an increased risk of future VTE in this large prospective cohort study. Compared to eGFR_{Cr-CysC} $\geq$ 90 mL/min/1.73 m², an eGFR_{Cr-CysC} <45 ml/min/1.73m² was associated with a 2-fold increased risk of VTE, after adjusting for demographic and VTE risk factors. This relationship was similar for provoked VTE, but the association was not statistically significant in unprovoked VTE. The association of VTE and eGFR appeared to vary by race and region, but power limited the interpretation of these analyses. There was no association between ACR and incident VTE. The cause-specific HRs for mortality were higher for each eGFR or ACR category than the risk for VTE. The population attributable fraction of VTE for CKD was modest compared to that for accepted clinical cut points for BMI and older age.

Our results provide further evidence supporting the relationship between eGFR and VTE.^{7, 9, 11, 21, 22} A meta-analysis of five studies, the largest work thus far, demonstrated an association between eGFR and VTE risk¹¹ and our findings extend this finding to a large, contemporary US cohort. We hypothesized that different eGFR equations used in previous research, including individual studies from the meta-analysis, may have led to conflicting results on the association of kidney disease measures and VTE. In the ARIC (Atherosclerosis Risk in Communities) and PREVEND (Prevention of Renal and Vascular Endstage Disease) studies, eGFR_{Cr} as determined by the MDRD Study equation was not associated with future VTE,^{7, 9} however, in ARIC, eGFR_{CysC} was associated with VTE. We

were able to clarify the relationship between kidney disease measures and VTE by simultaneously comparing the relationships of the CKD-EPI (eGFR_{Cr}, eGFR_{CysC}, eGFR_{Cr-CysC}) and MDRD Study eGFR equations, and ACR, with VTE risk in one study. eGFR_{Cr}, eGFR_{Cr-CysC} and MDRD Study-based eGFR_{Cr} were all significantly associated with VTE risk, in sum, supporting a link between kidney disease measures and VTE. With regards to type of VTE, the association of eGFR <45 ml/min/1.73m² was somewhat stronger for provoked VTE than unprovoked. Uniformly, the risk of VTE begins at an eGFR below 45 ml/min/1.73m², suggesting the mechanism of the association between eGFR and VTE could relate to changes that occur at this level of clearance.

In contrast to eGFR, ACR was not associated with VTE in this study. This is consistent with the finding in ARIC, the only other epidemiologic study of the relationship of ACR and VTE risk performed in the United States.⁹ In the PREVEND study, a Dutch cohort that oversampled for albuminuria, urinary albumin excretion was associated with increased risk of future VTE. Differences in the cohort composition compared to the REGARDS and ARIC studies could account for the different results. In PREVEND there were more smokers (38% versus 14%), fewer diabetics (4% versus 20%) and participants had lower BMI (mean BMI, 26.1 versus 29.2 kg/m²) compared to REGARDS, and people with insulin-treated diabetes were excluded.

Race and regional differences in the risk of VTE have been previously reported in the REGARDS study.¹⁶ Therefore, we studied whether race modified the association of eGFR and VTE within region (southeast/non-southeast). The association of eGFR and VTE appeared largest in whites residing outside of the southeast. While this may have been a chance finding and power to detect two-way interactions was limited, the reason for this finding may be due to the competing risk for death. For eGFR < 45 ml/min/1.73m², whites outside the southeast had the lowest cause-specific HR for death, compared to whites in the southeast or blacks in either region. In the aforementioned meta-analysis, there was no difference in the association of kidney disease and VTE by race. Conflicting results may be related to different definitions of kidney disease and limited number of black participants residing outside of the southeast included in the meta-analysis.

There are several strengths of the current study. The large, prospective, population based nature of the study enables our results to be generalized to black and white Americans living across a geographically diverse region of the United States. We were able to compare associations of kidney disease measures with VTE using several different equations in one study. The study was a contemporary cohort reflecting current trends in obesity and medication use (including widespread use of statins) that might alter relationships of CKD with VTE, and reflects current diagnosis patterns for VTE, which have changed over the past few decades.²³ The presentation of competing risk of death is unique in the study of kidney disease measures and VTE, and informed our understanding of potential race and regional differences in the risk of VTE.

Limitations of this study require consideration. As with many other prospective cohort studies of general populations, GFR was estimated and not measured. The estimates of GFR and ACR were obtained once at baseline. This could have led to misclassification. The

PREVEND study reported that ACR was less accurate and more biased than eAER,²⁴ because urinary creatinine is influenced by muscle mass, introducing confounding based on non-albuminuric covariates.²⁵ However, in a sensitivity analysis our results were consistent when utilizing eAER as a predictor. Our analysis may have been limited by low power to detect smaller differences in risk of VTE by ACR category. With 239 VTE events and a prevalence of 14% ACR ≥ 30 mg/g, we estimated 80% power to detect an HR of 1.7 or higher using $\alpha < 0.05$. Despite a large cohort of blacks and whites, power was limited in studying both race and region stratified associations of kidney disease measures and VTE. The results may not be generalizable to the entire US population as REGARDS was limited to self-identified black and white participants aged 45 years or older. Finally, while we adjusted for factors known to be associated with VTE risk the results could be influenced by unmeasured factors and residual confounding could exist.

The present prospective study provides further clarification on a growing literature supporting a relationship between kidney function and VTE. In our study, eGFR < 45 ml/min/1.73m² was associated with a two-fold risk of VTE and a three-fold risk of mortality. Further study of the mechanisms of the association between low eGFR and VTE and potential modifiable risk factors is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

A full list of participating REGARDS investigators and institutions can be found at www.regardsstudy.org.

The authors thank the other investigators, the staff, and the participants of the REGARDS study for their valuable contributions. Additional thanks to Dr Virginia Hood for her important contributions to this manuscript as a member of Dr. Cheung's dissertation committee.

Support: This study was supported by cooperative agreement U01 NS041588 (G. Howard, Principal Investigator) from the National Institute of Neurological Disorders and Stroke and additional funding from American Recovery and Reinvestment Act grant RC1HL099460 (N. Zakai, Principal Investigator) from the National Heart, Lung, and Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke ; the National Heart, Lung, and Blood Institute; or the National Institutes of Health. Representatives of the funding agency were not directly involved in the collection, management, analysis or interpretation of the data. An unrestricted educational grant from Amgen Corporation funded cystatin C and ACR measurements. The funders had no role in the study design, collection, analysis, interpretation; writing the report nor decision to submit the report for publication.

References

1. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007; 298(17):2038–2047. [PubMed: 17986697]
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. The New England journal of medicine. 2004; 351(13):1296–1305. [PubMed: 15385656]
3. Kayali F, Najjar R, Aswad F, Matta F, Stein PD. Venous thromboembolism in patients hospitalized with nephrotic syndrome. The American journal of medicine. 2008; 121(3):226–230. [PubMed: 18328307]

4. Tveit DP, Hypolite IO, Hsieh P, et al. Chronic dialysis patients have high risk for pulmonary embolism. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2002; 39(5):1011–1017. [PubMed: 11979344]
5. Abbott KC, Cruess DF, Agodoa LY, Sawyers ES, Tveit DP. Early renal insufficiency and late venous thromboembolism after renal transplantation in the United States. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2004; 43(1):120–130. [PubMed: 14712435]
6. Poli D, Zanazzi M, Antonucci E, et al. Renal transplant recipients are at high risk for both symptomatic and asymptomatic deep vein thrombosis. *Journal of thrombosis and haemostasis : JTH*. 2006; 4(5):988–992. [PubMed: 16689749]
7. Mahmoodi BK, Gansevoort RT, Veeger NJ, et al. Microalbuminuria and risk of venous thromboembolism. *JAMA : the journal of the American Medical Association*. 2009; 301(17):1790–1797. [PubMed: 19417196]
8. Wattanakit K, Cushman M, Stehman-Breen C, Heckbert SR, Folsom AR. Chronic kidney disease increases risk for venous thromboembolism. *Journal of the American Society of Nephrology : JASN*. 2008; 19(1):135–140. [PubMed: 18032796]
9. Folsom AR, Lutsey PL, Astor BC, Wattanakit K, Heckbert SR, Cushman M. Chronic kidney disease and venous thromboembolism: a prospective study. *Nephrol Dial Transplant*. 2010; 25(10):3296–3301. [PubMed: 20353958]
10. Office of the Surgeon General (US); National Heart L, Blood Institute (US). [Accessed November 26, 2013] The Surgeon General's Call to Action to Prevent Deep Venous Thrombosis and Pulmonary Embolism. 2008. <http://www.ncbi.nlm.nih.gov/books/NBK44178/>.
11. Mahmoodi BK, Gansevoort RT, Naess IA, et al. Association of mild to moderate chronic kidney disease with venous thromboembolism: pooled analysis of five prospective general population cohorts. *Circulation*. 2012; 126(16):1964–1971. [PubMed: 22977129]
12. Howard VJ, Cushman M, Pulley L, et al. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology*. 2005; 25(3):135–143. [PubMed: 15990444]
13. Gillett SR, Boyle RH, Zakai NA, McClure LA, Jenny NS, Cushman M. Validating laboratory results in a national observational cohort study without field centers: the Reasons for Geographic and Racial Differences in Stroke cohort. *Clinical biochemistry*. 2014; 47(16–17):243–246. [PubMed: 25130959]
14. Kurella Tamura M, Wadley V, Yaffe K, et al. Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2008; 52(2):227–234. [PubMed: 18585836]
15. Inker LA, Schmid CH, Tighiouart H, et al. Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. *New England Journal of Medicine*. 2012; 367(1):20–29. [PubMed: 22762315]
16. Zakai NA, McClure LA, Judd SE, et al. Racial and Regional Differences in Venous Thromboembolism in the United States in Three Cohorts. *Circulation*. 2014
17. Banach M, Bromfield S, Howard G, et al. Association of systolic blood pressure levels with cardiovascular events and all-cause mortality among older adults taking antihypertensive medication. *International journal of cardiology*. 2014; 176(1):219–226. [PubMed: 25085381]
18. Halanych JH, Shuaib F, Parmar G, et al. Agreement on cause of death between proxies, death certificates, and clinician adjudicators in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *American journal of epidemiology*. 2011; 173(11):1319–1326. [PubMed: 21540327]
19. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *American journal of epidemiology*. 2009; 170(2):244–256. [PubMed: 19494242]
20. Ix JH, Wassel CL, Stevens LA, et al. Equations to Estimate Creatinine Excretion Rate: The CKD Epidemiology Collaboration. *Clinical Journal of the American Society of Nephrology*. 2011; 6(1):184–191. [PubMed: 20966119]

21. Ocak G, Lijfering WM, Verduijn M, et al. Risk of venous thrombosis in patients with chronic kidney disease: identification of high-risk groups. *Journal of thrombosis and haemostasis : JTH*. 2013; 11(4):627–633. [PubMed: 23433091]
22. Ocak G, Vossen CY, Lijfering WM, et al. Role of hemostatic factors on the risk of venous thrombosis in people with impaired kidney function. *Circulation*. 2014; 129(6):683–691. [PubMed: 24211824]
23. Huisman MV, Klok FA. Diagnostic management of acute deep vein thrombosis and pulmonary embolism. *Journal of thrombosis and haemostasis : JTH*. 2013; 11(3):412–422. [PubMed: 23294863]
24. Abdelmalek JA, Gansevoort RT, Lambers Heerspink HJ, Ix JH, Rifkin DE. Estimated albumin excretion rate versus urine albumin-creatinine ratio for the assessment of albuminuria: a diagnostic test study from the Prevention of Renal and Vascular Endstage Disease (PREVEND) Study. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2014; 63(3):415–421. [PubMed: 24364894]
25. Younes N, Cleary PA, Steffes MW, et al. Comparison of urinary albumin-creatinine ratio and albumin excretion rate in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. *Clinical journal of the American Society of Nephrology : CJASN*. 2010; 5(7):1235–1242. [PubMed: 20448066]

Figure 1.

Flow diagram of participants included in the study. Non-mutually exclusive counts in parentheses.

Table 1Baseline characteristics by eGFR_{cr-cys} categories

Characteristic	eGFR _{cr-cys} , ml/min/1.73m ²			
	90 (n=14,087)	60–<90 (n=8,670)	45–<60 (n=8,670)	<45 (n=870)
Mean age, y	61.0±8.1	68.5±8.6	72.5±8.8	72.1±9.1
Female sex	64.4	40.9	38.2	38.5
Black race	35.5	44.6	48.1	54.7
SE Region of Residence	57.3	53.4	52.3	51.7
Hypertension	48.9	67.0	80.1	87.3
Diabetes	16.1	22.0	34.7	47.5
Hyperlipidemia	42.1	46.7	51.7	54.4
CVD	11.1	22.5	37.5	44.0
BMI, kg/m ²	28.9±6.1	29.4±6.0	29.7±6.2	30.1±7.0
Smoking				
Current	14.9	13.6	12.8	12.1
Former	47.9	42.0	41.2	42.2
Never	37.1	44.4	46.0	45.7
Statin use	27.0	34.5	43.6	47.0
Aspirin use	37.8	48.7	53.7	57.2
Hormone therapy use*	19.2	11.3	11.1	6.9
Warfarin use	1.4	3.7	7.1	7.7
Serum creatinine (mg/dL)	0.7±0.1	1.0±0.2	1.3±0.2	0.9±0.8
Serum cystatin C (mg/L)	0.8±0.1	1.1±0.1	1.4±0.2	2.1±0.7
eGFR _{cr} (ml/min/1.73m ²)	96±13	78±13	56±10	37±12
eGFR _{cys} (ml/min/1.73m ²)	102±14	72±13	49±9	31±9
Urine ACR (mg/g)	20±108	45±316	123±447	440±987

Note: Values for categorical variables are given as percentage; values for continuous variables, as mean ± standard deviation. Conversion factor for serum creatinine in mg/dL to μmol/L, ×88.4.

ACR, albumin-creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; eGFR_{cr}, creatinine-based estimated glomerular filtration rate; eGFR_{cys}, cystatin C-based estimated glomerular filtration rate; eGFR_{cr-cys}, creatinine and cystatin C-based estimated glomerular filtration rate; SE, Southeast

* Hormone therapy use for women only.

Table 2

Baseline characteristics by ACR categories

Characteristic	ACR, mg/g			
	<10 (n=15,777)	10–<30 (n=5,696)	30–<300 (n=2,961)	300 (n=668)
Age, y	63.4±9.0	66.5±9.5	67.3±9.9	66.6±9.3
Female sex	52.9	59.3	50.4	42.4
Black race	37.7	39.5	48.1	63.5
SE Region of Residence	55.5	56.5	54.3	53.3
Hypertension	51.44	65.5	75.2	87.4
Diabetes	13.8	25.0	37.4	60.45
Hyperlipidemia	42.6	46.4	48.7	59.0
CVD	14.1	20.9	26.3	37.7
BMI, kg/m ²	28.9±5.8	29.2±6.4	30.2±6.6	30.7±7.0
Smoking				
Current	13.2	14.7	17.6	20.7
Former	46.6	44.8	41.8	33.5
Never	40.2	40.5	40.6	44.7
Statin use	29.0	33.3	36.3	44.5
Aspirin use	41.3	45.4	46.8	52.9
Hormone therapy use *	19.4	12.2	11.7	8.0
Warfarin use	2.0	3.4	4.7	4.6
Serum creatinine (mg/dL)	0.9±0.2	0.9±0.3	1.0±0.4	1.5±1.0
Serum cystatin C (mg/L)	0.9±0.2	1.0±0.3	1.1±0.4	1.6±0.9
eGFR _{cr} (ml/min/1.73m ²)	87±17	85±20	81±24	62±29
eGFR _{cys} (ml/min/1.73m ²)	90±22	84±24	76±27	55±28
Urine ACR (mg/g)	5±2	16±5	84±60	1224±1422

Note: Values for categorical variables are given as percentage; values for continuous variables, as mean ± standard deviation. Differences were significant (p <0.05) across categories of ACR for all variables except region of residence. Conversion factor for serum creatinine in mg/dL to μmol/L, ×88.4.

ACR, albumin-creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; eGFR_{cr}, creatinine-based estimated glomerular filtration rate; eGFR_{cys}, cystatin C-based estimated glomerular filtration rate; SE, Southeast

* Hormone therapy use for women only.

Table 3

Adjusted Incidence Rate for VTE and mortality per 1000 Person-Years by kidney disease measures

eGFR _{cr-cys}	90 ml/min/1.73m ²	60–<90 ml/min/1.73m ²	45–<60 ml/min/1.73m ²	<45 ml/min/1.73m ²	P for trend
No. at risk	14,087	8,670	1,475	870	
Person-time	66,171	41,580	6,788	3,720	
No. with VTE	90	110	21	18	
VTE IR (95% CI)	1.50 (1.21, 1.85)	2.14 (1.72, 2.66)	2.18 (1.38, 3.46)	3.43 (2.09, 5.63)	0.02
No. of deaths	666	1,132	428	378	
Mortality IR (95% CI)	11.4 (10.6, 12.3)	18.5 (17.2, 19.8)	33.5 (30.0, 37.4)	53.4 (47.4, 60.1)	<0.001
ACR					
	<10 mg/g	10–<30 mg/g	30–<300 mg/g	300 mg/g	<i>P</i>
No. at risk	15,777	5,696	2,961	668*	
Person-time	75,273	26,732	13,347	2907	
No. with VTE	135	62	36	6	
VTE IR (95% CI)	1.69 (1.42, 2.02)	1.97 (1.52, 2.56)	2.16 (1.54, 3.04)	1.70 (0.76, 3.81)	0.5
No. of deaths	1,020	738	601	245	
Mortality IR (95% CI)	11.4 (10.7, 12.2)	19.1 (17.6, 20.6)	28.0 (25.6, 30.7)	54.6 (47.8, 62.2)	<0.001

Note: Incidence rates are adjusted for age, sex and race.

ACR, albumin-creatinine ratio; CI, confidence interval; eGFR_{cr-cys}, creatinine and cystatin C–based estimated glomerular filtration rate; IR, incidence rate; VTE, venous thromboembolism

* Of the 50 participants with ACR>3000 mg/g only one VTE in this category.

Table 4

Cause-specific hazard ratios for total, provoked, and unprovoked VTE and mortality by kidney disease measures

eGFR _{cr-cys}				
	60–<90 ml/min/1.73m ²	45–<60 ml/min/1.73m ²	<45 ml/min/1.73m ²	p for trend
Crude VTE HR (95% CI)	1.91 (1.45, 2.51)	2.24 (1.41, 3.57)	3.38 (2.04, 5.60)	<0.001
Adjusted VTE HR (95% CI)				
Total	1.28 (0.94, 1.76)	1.30 (0.77, 2.18)	2.13 (1.21, 3.76)	0.01
Provoked	1.13 (0.73, 1.75)	1.39 (0.69, 2.79)	2.31 (1.07, 4.96)	0.03
Unprovoked	1.47 (0.93, 2.32)	1.20 (0.55, 2.64)	1.98 (0.86, 4.61)	0.2
Crude mortality HR (95% CI)	2.53 (2.29, 2.78)	6.09 (5.39, 6.89)	10.04 (8.84, 11.41)	<0.001
Adjusted mortality HR (95% CI)	1.40 (1.26, 1.57)	2.28 (1.97, 2.64)	3.18 (2.72, 3.71)	<0.001
ACR				
	10–<30 mg/g	30–<300 mg/g	300 mg/g	p for trend
Crude VTE HR (95% CI)	1.30 (0.96, 1.76)	1.54 (1.06, 2.22)	1.18 (0.52, 2.66)	0.6
Adjusted VTE HR (95% CI)				
Total	1.14 (0.84, 1.55)	1.15 (0.79, 1.68)	0.65 (0.26, 1.64)	0.4
Provoked	1.38 (0.91, 2.09)	1.42 (0.85, 2.36)	0.53 (0.13, 2.25)	0.4
Unprovoked	1.92 (0.58, 1.45)	0.92 (0.52, 1.64)	0.78 (0.24, 2.59)	0.7
Crude mortality HR (95% CI)	2.07 (1.88, 2.28)	3.41 (3.08, 3.78)	6.42 (5.58, 7.40)	<0.001
Adjusted mortality HR (95% CI)	1.46 (1.32, 1.62)	1.94 (1.74, 2.20)	2.60 (2.20, 3.06)	<0.001

Note: The reference categories are 90 mL/min/1.73 m² for eGFR_{cr-cys} and <10 mg/g for ACR. VTE Cox models are adjusted for age, sex, race × region, body mass index. Cox models for mortality are additionally adjusted for hypertension, diabetes, hyperlipidemia, cardiovascular disease and smoking. Adjusted ACR models are adjusted for estimated glomerular filtration rate and vice versa.

ACR, albumin-creatinine ratio; CI, confidence interval; eGFR_{cr-cys}, creatinine and cystatin C–based estimated glomerular filtration rate; HR, hazard ratio; VTE, venous thromboembolism

Table 5

Adjusted Cause-Specific Hazard Ratios for VTE and mortality by eGFR_{cr-cys} stratified by region and race

	Region of Residence	Race	eGFR _{cr-cys} mL/min/1.73m ²			p for trend	P for interaction race × eGFR
			60–<90	45–<60	<45		
VTE							
	Southeast	White	1.21 (0.72, 2.03)	0.30 (0.07, 1.31)	1.95 (0.76, 4.99)	0.7	} 0.1
		Black	2.18 (1.06, 4.46)	3.45 (1.28, 9.31)	1.68 (0.36, 7.82)	0.4	
	Non-southeast	White	1.09 (0.61, 1.97)	1.64 (0.64, 4.11)	3.37 (1.34, 8.45)	0.007	} 0.7
		Black	0.89 (0.39, 2.02)	1.05 (0.33, 3.33)	1.04 (0.26, 4.10)	0.9	
Mortality							
	Southeast	White	1.44 (1.20, 1.72)	2.25 (1.76, 2.88)	3.03 (2.31, 3.98)	<0.001	} <0.001
		Black	1.24 (0.95, 1.60)	1.99 (1.41, 2.81)	3.15 (2.20, 4.50)	<0.001	
	Non-southeast	White	1.33 (1.06, 1.66)	2.12 (1.59, 2.84)	2.29 (1.64, 3.19)	<0.001	} <0.001
		Black	1.46 (1.14, 1.88)	2.37 (1.73, 3.25)	3.36 (2.40, 4.69)	<0.001	

Note: The reference category is 90 mL/min/1.73 m². VTE HRs are adjusted for age, sex and body mass index. Mortality HRs are additionally adjusted for hypertension, diabetes, hyperlipidemia, cardiovascular disease, smoking and albuminuria.

ACR, albumin-creatinine ratio; CI, confidence interval; eGFR< estimated glomerular filtration rate; eGFR_{cr-cys}, creatinine and cystatin C–based estimated glomerular filtration rate; HR, hazard ratio; VTE, venous thromboembolism