Chronic kidney disease and venous thromboembolism: a prospective study

Aaron R. Folsom1, Pamela L. Lutsey1, Brad C. Astor2, Keattiyoat Wattanakit3, Susan R. Heckbert4, Mary Cushman5,6 for the Atherosclerosis Risk in Communities (ARIC) Study

1Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA, 2Department of Epidemiology, The Johns Hopkins Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, MD, USA, 3Department of Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA, 4Department of Epidemiology, University of Washington, Seattle, WA, USA, 5Department of Medicine, University of Vermont, Burlington, VT, USA and 6Department of Pathology, University of Vermont, Burlington, VT, USA

Correspondence and offprint requests to: Aaron R. Folsom; E-mail: folso001@umn.edu

Abstract

Background. The incidence of venous thromboembolism (VTE) is increased with severe kidney disease, but whether less-severe chronic kidney disease (CKD) increases the risk of VTE is less certain.

Methods. We studied this in a prospective cohort of 10,700 whites and African Americans, aged 53–75 years, attending Visit 4 (1996–98) of the Atherosclerosis Risk in Communities Study. Estimated glomerular filtration rate (eGFR) values were estimated from prediction equations based on serum creatinine (eGFRcreat) or cystatin C (eGFRcys). Normal kidney function was defined as eGFR ≥90 ml/min/1.73 m² and mildly decreased kidney function as eGFR between 60 and 89 ml/min/1.73 m² and Stage 3 to 4 CKD as eGFR between 15 and 59 ml/min/1.73 m². VTE occurrence (n = 228) was ascertained over a median of 8.3 years.

Results. For eGFRcys, the age-, race- and sex-adjusted hazard ratios of total VTE were 1.0, 1.40 and 1.94 (P trend = 0.003) for normal kidney function, mildly impaired kidney function and Stage 3 to 4 CKD, respectively. These respective hazard ratios were moderately attenuated to 1.0, 1.26 and 1.60 (P trend = 0.04) with adjustment for hormone replacement therapy, diabetes and body mass index. Associations between CKD based on eGFRcreat and VTE were slightly stronger for idiopathic VTE than for secondary VTE. In contrast, CKD based on eGFRcys was not associated with total VTE occurrence.

Conclusions. Stage 3 to 4 CKD, based on eGFRcys but not eGFRcreat, was associated with an approximately 1.6-fold increased risk of VTE.

Keywords: chronic kidney disease; prospective study; pulmonary embolism; venous thromboembolism

Introduction

The incidence of venous thromboembolism (VTE), comprising venous thrombosis and pulmonary embolism, is increased in patients with end-stage renal disease (ESRD) or end-stage renal failure (ESRF). This increased risk is greater for patients with ESRF who are undergoing maintenance therapy, diabetes and body mass index. Associations between CKD based on eGFRcreat and VTE were slightly stronger for idiopathic VTE than for secondary VTE. In contrast, CKD based on eGFRcys was not associated with total VTE occurrence.

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nephrotic syndrome, in those undergoing dialysis and in those with a renal transplant [1–5]. Whether less-severe forms of chronic kidney disease (CKD) increase the risk of VTE is less certain. We recently reported in the Longitudinal Investigation of Thromboembolism Etiology (LITE) that, compared with normal kidney function, the relative risk of VTE was 1.71 [95% confidence intervals (95% CI) = 1.18–2.49] for adults with Stage 3 or 4 CKD based on an estimated glomerular filtration rate (eGFR) derived from serum creatinine [6]. In contrast, VTE was not related to CKD defined by eGFR derived from cystatin C in a subset of older LITE subjects [6]. In a Dutch cohort, lower eGFR derived from creatinine was also univariately associated with an increased risk of VTE, but not after adjustment for age and sex [7].

The measurement of both creatinine and cystatin C in the fourth Atherosclerosis Risk in Communities (ARIC) Study examination offered an opportunity to re-examine the association of CKD with VTE.

**Materials and methods**

In 1987–89, the ARIC Study recruited to a baseline examination a cohort of 15 792 men and women aged 45–64 years, predominantly whites or African Americans, from four US communities [8]. Participants were re-examined in 1990–92 (93% response), 1993–95 (86%) and 1996–98 (80%). Participants in the ARIC Visit 4 examination served as the cohort for the present analysis. At ARIC Visit 4, body mass index (BMI) was assessed as weight (in kilograms) in a scrub suit divided by height (in metres) squared. Use of hormone replacement therapy (HRT) was recorded. Diabetes was defined as non-fasting glucose ≥126 mg/dl after a 10-h overnight fast or non-fasting glucose ≥200 mg/dl or a physician’s diagnosis or treatment for diabetes. Albuminuria and an untimed urine sample were stored at −70°C.

Serum creatinine was measured within a few weeks after ARIC Visit 4 using a modified kinetic Jaffé reaction. Approximately 4% of samples were split and measured as blinded replicates on different dates to assess repeatability. The reliability coefficient for blinded quality control replicates of serum creatinine was 0.95 (459 blinded replicates). Creatinine values were calibrated using regression to the Cleveland Clinic Laboratory [9,10], and eGFR based on creatinine (eGFRcreat) was then calculated using the equations recently developed by Levey et al. [11]. As a sensitivity analysis, we also used eGFR based on the more familiar Modification of Diet in Renal Disease (MDRD) Study four-variable equation [12]; results were somewhat weaker using the MDRD formula.

Cystatin C was measured on Visit 4 serum in 2008 by a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring, Inc., Deerfield, IL) with a BNII nephelometer (Dade Behring, Inc., Deerfield, IL) [13,14]. The reliability coefficient for blinded quality control replicates of cystatin C was 0.65 (421 blinded replicates), but after removing 10 replicate pair outliers (>3 SD), the reliability was 0.94 (n = 411). We calibrated ARIC cystatin C to the Cleveland Clinic after a small (n = 40) study found a relatively constant 16% difference (i.e. Cleveland Clinic = 1.16 × ARIC). Then, we calculated eGFR by cystatin C (eGFRcys) using the Chronic Kidney Disease Epidemiology Collaboration equation [15]: eGFRcys (ml/min/1.73 m²) = 127.7 × cystatin C (mg/dl)¹.17 × age⁻⁰.91 (if female) × 1.06 (if black).

CKD was categorized, using eGFRcreat and eGFRcys separately, on the basis of the National Kidney Foundation guidelines: eGFR < 60 ml/min/1.73 m² for normal kidney function, eGFR between 60 and 89 ml/min/1.73 m² for mildly decreased kidney function and eGFR between 15 and 59 ml/min/1.73 m² for Stage 3 or 4 CKD. Urinary creatinine and albumin were measured in 2003–04. Albumin was measured by a nephelometric method either on the Dade Behring BN100 (Dade Behring, Inc., Deerfield, IL; assay sensitivity, 2.0 mg/L) or Beckman Image Nephelometer (Beckman Coulter, Inc., Fullerton, CA), and creatinine was measured by the Jaffé method. Albumin–creatinine ratio (ACR) was calculated, and total albuminuria was categorized as the sum of microalbuminuria (ACR 30–299 mg/g) and macroalbuminuria (ACR ≥300 mg/g) [10]. Blinded split samples (n = 516) analysed for reliability showed a correlation coefficient (r) for log-transformed ACR of r = 0.95.

Factor VIIa and activated partial thromboplastin time (aPTT) were VTE risk factors in ARIC [16,17] but were not measured at Visit 4, so the Visit 1 value was used. Factor V Leiden and the prothrombin G20210A polymorphism were not measured in the whole ARIC cohort, but rather only in a small subset and, therefore, not used in these analyses.

ARIC participants were followed up from Visit 4 (1996–98, n = 11 573) through 2005 to identify hospitalized VTE events. These were validated by physician review using a standardized protocol and subcategorized as idiopathic or secondary (occurring within 90 days of major trauma, surgery, marked immobility, active cancer or chemotherapy) [18]. A total of 263 VTE events were identified. Approximately one-third of these had been included in our previous ARIC analysis [6], which examined baseline (1987–89) eGFRcreat and VTE through 2001. We did not exclude the overlapping VTE events from this report because the 1996–98 eGFR measurements were made independently from the 1987–89 eGFR measurements and results were similar whether or not they were excluded.

Our hypothesis was that CKD by eGFRcreat or eGFRcys in 1996–98 would be positively associated with VTE incidence. From the 11 573 participants at Visit 4, we excluded 342 who had a prior history of VTE by Visit 4 and 204 who were taking warfarin. We also excluded those with missing exposure variables or with severe CKD (eGFR < 15 ml/min/1.73 m²). eGFRcreat (n = 120) and eGFRcys (n = 344). Excluded numbers were not mutually exclusive. Our final analytic sample included 10 700 participants, among whom there were 8317 whites, 2353 African Americans and 30 others who were grouped with African Americans for this analysis. Follow-up time ended when the participant had a VTE, died, was lost to follow-up, or survived until 31 December 2005.

Cox proportional hazards regression was used to model the association between exposure variables and VTE incidence and to derive hazard ratios and 95% CI. Covariates included previous VTE risk factors measured in the whole ARIC cohort, measured at Visit 4 unless otherwise specified: age (continuous), race (African American, white), sex/HRT (men, women taking HRT, women not taking HRT), diabetes (yes, no), BMI (continuous), Visit 1 Factor VIII, and Visit 1 aPTT. Poisson regression models were used to compute adjusted incidence rates and 95% CI.

**Results**

In this sample of 10 700 ARIC Visit 4 participants, aged 53–75 years, with no history of VTE and no current warfarin use, the Pearson correlation between eGFRcys and eGFRcreat (r = 0.46) and overlap of CKD categories was moderate (Table 1). Based on eGFRcys, 29% of participants had normal kidney function, 59% had mildly decreased kidney function and 13% had Stage 3 or 4 CKD. Based on eGFRcreat, these percentages were 40, 54 and 6%, respectively. A total of 72 of these participants subsequently developed ESRD, defined as starting dialysis, receiving a kidney transplant or dying from kidney failure.

<table>
<thead>
<tr>
<th>eGFRcreat (ml/min/1.73 m²)</th>
<th>290</th>
<th>60–89</th>
<th>15–59</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFRcreat (ml/min/1.73 m²)</td>
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<td>999</td>
<td>15</td>
<td>3088</td>
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<tr>
<td>60–89</td>
<td>2049</td>
<td>4005</td>
<td>211</td>
<td>6265</td>
</tr>
<tr>
<td>15–59</td>
<td>150</td>
<td>765</td>
<td>432</td>
<td>1347</td>
</tr>
<tr>
<td>Total</td>
<td>4273</td>
<td>5769</td>
<td>658</td>
<td>1070</td>
</tr>
</tbody>
</table>

Weighted kappa = 0.35 (95% CI = 0.34, 0.37) for agreement between eGFRcys and eGFRcreat categories.
Approximately 70% of those developing ESRD had Stage 3 or 4 at ARIC Visit 4.

As shown in Table 2, lower eGFR_{cys} was associated with greater age, fewer men, more whites, less HRT use, greater BMI, greater Factor VIII and shorter aPTT. There was no trend in diabetes across the full spectrum of eGFR_{cys}, but diabetes prevalence was highest in those with Stage 3 or 4 CKD. Lower eGFR_{creat} (Table 2) was similarly associated with most of these risk factors but less clearly with sex or BMI.

Over a median of 8.3 years of follow-up after ARIC Visit 4, 2286 incident VTE events occurred (81 idiopathic, 147 secondary), yielding a crude total VTE incidence of 2.7/1000 person-years. The mean interval between eGFR assessment and VTE events was 4.9 years. For eGFR_{cys} (Table 3), the age-, race- and sex-adjusted hazard ratios of total VTE (Model 1) were 1.0, 1.40 and 1.94 (P trend = 0.003) for normal kidney function, mildly impaired kidney function and Stage 3 to 4 CKD, respectively. These hazard ratios were moderately attenuated to 1.0, 1.26 and 1.60 (P trend = 0.04) with adjustment for HRT, diabetes and BMI (Model 2); they became non-significant with adjustment for baseline Factor VIII and aPTT (Model 3). When Stage 3 and Stage 4 were analysed separately (not shown in Table 3), Model 2 VTE hazard ratios were 1.48 (95% CI = 0.92, 2.37) for Stage 3 and 2.85 (95% CI = 1.21, 6.75) for Stage 4 CKD (Stage 4 n = 154, with six VTE events). Four VTE events occurred among the 72 participants who had developed ESRD. Associations between CKD and VTE were slightly stronger for idiopathic VTE than for secondary VTE (Table 3). We also modelled

| Table 2. Participant characteristics in relation to glomerular filtration rate based on cystatin C (eGFR_{cys}) or creatinine (eGFR_{creat}), ARIC, 1996–98 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Characteristic                  | eGFR_{cys} (ml/min/1.73 m^2) |                      |                      |                      |                      |                      |
|                                | ≥90 (n = 3088)     | 60–89 (n = 6265)   | 15–59 (n = 1347)    | P-trend           |
| Age, years (SD)                 | 60.5 (5.1)         | 63.2 (5.6)         | 65.8 (5.4)         | <0.0001          |
| Male, n (%)                     | 1451 (47.0)        | 2732 (43.6)        | 530 (39.4)         | <0.0001          |
| African Americans, n (%)        | 1198 (38.8)        | 988 (15.8)         | 197 (14.6)         | <0.0001          |
| HRT use, n (%)                  | 567 (34.6)         | 882 (25.0)         | 155 (19.0)         | <0.0001          |
| BMI, kg/m^2 (SD)                | 27.7 (4.9)         | 28.9 (5.5)         | 30.1 (6.3)         | <0.0001          |
| Diabetes, n (%)                 | 566 (18.5)         | 884 (14.2)         | 293 (21.8)         | 0.7              |
| Factor VIII, % (SD)             | 124 (36)           | 127 (35)           | 140 (41)           | <0.0001          |
| aPTT, seconds (SD)              | 29.3 (2.9)         | 29.1 (3.0)         | 28.9 (3.1)         | 0.0005           |

| Table 3. Hazard ratio (95% CI) of VTE incidence in relation to glomerular filtration rate derived from cystatin C (eGFR_{cys}), ARIC, 1996–2005 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Characteristic                  | eGFR_{creat} (ml/min/1.73 m^2) |                      |                      |                      |                      |
|                                | ≥90 (n = 4273)   | 60–89 (n = 5769) | 15–59 (n = 658)   | P-trend           |
| Age, years (SD)                 | 60.4 (5.2)       | 64.0 (5.4)       | 66.8 (5.2)       | <0.0001          |
| Male, n (%)                     | 1812 (42.4)      | 2607 (45.2)      | 294 (44.7)       | 0.01             |
| African Americans, n (%)        | 1262 (29.5)      | 971 (16.8)       | 150 (22.8)       | <0.0001          |
| HRT use, n (%)                  | 710 (28.9)       | 823 (26.0)       | 71 (19.5)        | <0.0001          |
| BMI, kg/m^2 (SD)                | 29.0 (6.0)       | 28.4 (5.1)       | 29.3 (5.3)       | 0.007            |
| Diabetes, n (%)                 | 777 (18.3)       | 801 (13.9)       | 165 (25.2)       | 0.29             |
| Factor VIII, % (SD)             | 126 (35)         | 128 (36)         | 139 (42)         | <0.0001          |
| aPTT, seconds (SD)              | 29.2 (3.1)       | 29.1 (2.9)       | 28.8 (2.9)       | 0.004            |

Model 1, adjusted for age (continuous), sex and race; Model 2, adjusted for age (continuous), sex and HRT use (three-level categorical variable), race, diabetes status and BMI (continuous); Model 3, adjusted for Model 2 plus Factor VIII (continuous) and aPTT (continuous).
Discussion

In the prospective population-based ARIC Study, Stage 3 to 4 CKD defined by eGFR\textsubscript{cys} of 15–59 ml/min/1.73 m\textsuperscript{2} was associated with an approximately 1.6-fold significantly increased risk of VTE, compared with normal kidney function, after adjustment for age, race, HRT, diabetes and BMI. In contrast, CKD defined by eGFR\textsubscript{creat} groupings was not associated with VTE occurrence. However, this discrepancy partly related to how CKD was grouped by eGFR\textsubscript{creat} compared with eGFR\textsubscript{cys} because, when treated as continuous variables, eGFR\textsubscript{cys} and eGFR\textsubscript{creat} had similar associations with VTE. The agreement on CKD classification between eGFR\textsubscript{cys} and eGFR\textsubscript{creat} was not very high (kappa = 0.35; Table 1), with eGFR\textsubscript{creat}, as expected [11], classifying more subjects to higher eGFR categories. This is similar to the kappa = 0.36 found in a recent study using data from the Third National Health and Nutrition Examination Survey [19]. In general, eGFR\textsubscript{cys} is believed to be a more accurate marker of kidney function because, when treated as continuous variables, eGFR\textsubscript{cys} and eGFR\textsubscript{creat} had similar associations with VTE. The association between eGFR\textsubscript{cys} and VTE may be a reflection of the true association between decreased kidney function and VTE.

These findings contrast somewhat with early follow-up of the LITE project, which comprises ARIC and the Cardiovascular Health Study (CHS) [6]. In LITE, Stage 3 to 4 CKD based on eGFR\textsubscript{creat}, using the MDRD equation [12], was associated with 1.7-fold increased VTE risk. In contrast, in CHS by itself, eGFR\textsubscript{cys} was not associated with VTE [6]; however, statistical power was low for CHS alone. Reasons for the discrepancy between the earlier LITE find-
ings and the current ARIC findings for eGFR\textsubscript{creat} categories of CKD are unclear. The cohorts are ageing and become less population-based as dropouts occur due to death and attrition. The laboratories measuring creatinine at baseline and ARIC Visit 4 were also different. There may also be an unknown confounding factor that explains the discrepancy. In both the prior report [6] and the present report, there was at least some evidence that CKD increases VTE risk, based on a continuous expression of eGFR\textsubscript{creat}.

The only other prospective, population-based study on this topic involved a Dutch cohort oversampled for albuminuria [7]; it found a univariate inverse association between eGFR\textsubscript{creat} and VTE incidence that was not independent of age and sex. However, the Dutch study had only 129 VTE events and, therefore, had limited statistical power, as its age- and sex-adjusted hazard ratio for CKD of 1.65 (95\% CI = 0.79–3.35) was comparable to the ARIC Study. Taken as a whole, existing data suggest a relatively weak 60\% increased risk of VTE in Stage 3 to 4 CKD patients.

A comparison of Models 1 and 2 in Table 3 suggests that VTE and CKD are at least partially connected through risk factors in common, such as ethnicity, obesity, diabetes and secondary causes of VTE. Nevertheless, the fact that Model 3 adjustment for Factor VIII and aPTT attenuated the CKD and VTE association suggests that coagulation abnormalities in CKD [23,24] may partly account for the increased VTE risk of CKD patients.

The Dutch study [7] found a strong positive association between albuminuria and incident VTE, with albuminuria measured by two 24-h urine samples or by a spot urine sample. In contrast, the ARIC Study found no association between VTE and the ACR in a spot urine sample. A relatively low prevalence of albuminuria may have limited our power to detect any association with VTE, but further research is warranted.

Other drawbacks of this study warrant consideration. First, although the ARIC Study is relatively large (n = 228 VTE events), statistical power was low for subgroup analyses and for detecting modest hazard ratios. Second, we employed only single measures of renal function; measurement error in the classification of CKD, deterioration of cystatin C samples stored at −70 °C for 10 years or changes in CKD status during follow-up would tend to obscure associations with VTE. Third, we had a very limited set of thrombotic risk factors for VTE in the full ARIC cohort and Factor VIII and aPTT were measured at an ARIC visit 9 years earlier. Nevertheless, those thrombotic markers were related to eGFR, so adjustment for their potential confounding effects seemed worthwhile even if suboptimal. Fourth, as with all epidemiologic studies of VTE, only clinically detected events were included. Finally, since the study population was aged 53–75 years, our results, strictly speaking, can be generalized only to these ages.

**Conclusion**

In summary, we found Stage 3 to 4 CKD, based on eGFR\textsubscript{cys} but not eGFR\textsubscript{creat}, to be associated with an approximately 1.6-fold increased risk of VTE.

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**Conflict of interest statement.** None declared.

**References**

Alcohol consumption and kidney function decline in the elderly

Vandana Menon¹, Ronit Katz², Kenneth Mukamal³, Bryan Kestenbaum⁴, Ian H. de Boer⁴, David S. Siscovick³, Mark J. Sarnak¹ and Michael G. Shlipak⁶

¹Division of Nephrology, Tufts Medical Center, Boston, MA, USA, ²Collaborative Health Studies Coordinating Center, Department of Biostatistics, University of Washington, Seattle, WA, USA, ³Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston, MA, USA, ⁴Division of Nephrology, ⁵Departments of Medicine and Epidemiology, University of Washington, Seattle, WA, USA, ⁶San Francisco VA Medical Center and University of California, San Francisco, CA, USA

Correspondence and offprint requests to: Vandana Menon, E-mail: vmenon@tuftsmedicalcenter.org

Abstract
Background. Alcohol consumption appears to be protective for cardiovascular disease; however, its relationship with kidney disease is unclear.

Methods. This prospective cohort study included 4343 subjects from the Cardiovascular Health Study, a longitudinal, community-based cohort of persons aged ≥65 from four US communities. We used previously defined categories based on weekly alcohol consumption: none, former, <1 drink, 1–6 drinks, 7–13 drinks and ≥14 drinks. Cystatin C was measured at baseline, year 3 and year 7; eligible subjects had at least two measures. Estimated GFR_{cys} was calculated from cystatin C. The primary outcome was rapid kidney function as an annual estimated GFR (eGFR_{cys}) loss >3 mL/min/1.73 m²/year.

Results. Eight percent of the cohort reported former alcohol use and 52% reported current alcohol consumption. During a mean follow-up of 5.6 years, 1075 (25%) participants had rapid kidney function decline. In adjusted logistic regression models, there was no association between alcohol use and kidney function decline (odds ratio, 95% confidence interval: none = reference; former = 1.18, 0.89–1.56; <1 drink = 1.20, 0.99–1.47; 1–6 = 1.18, 0.95–1.45; 7–13 = 1.10, 0.80–1.53; >14 = 0.89, 0.61–1.13). Results were similar with kidney function decline as a continuous outcome.

Conclusions. Our results suggest that moderate alcohol consumption has neither adverse nor beneficial effects on kidney function. Although clinicians will need to consider the potential deleterious effects associated with alcohol consumption, there does not appear to be a basis for recommending that older adults discontinue or initiate light to moderate alcohol consumption to protect against kidney disease.

Keywords: alcohol; kidney disease; outcomes; progression

Introduction
Cardiovascular disease (CVD) and chronic kidney disease (CKD) share pathophysiologic features, and several CVD risk factors are also risk factors for progression of CKD. While alcohol consumption appears to be protective for CVD, the relationship with kidney disease is complex. Alcohol may lead to kidney disease by directly damaging the kidney [1] or by elevating blood pressure [2]. Conversely,