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Original Investigation

Risk of Venous Thromboembolism in Patients by Albuminuria and Estimated GFR

David Massicotte-Azarniouch, MD,[1] Anan Bader Eddeen, MSc,[2] Alejandro LazoLanger, MD,[3,4] Amber O. Molnar, MD,[4,5] Ngan N. Lam, MD,[6] Megan K. McCallum, MPH,[4] Sarah Bota, MPH,[4] Deborah Zimmerman, MD,[1] Amit X. Garg, MD,[4,7] Ziv Harel, MD,[4,8] Jeffery Perl, MD,[4,8] Ron Wald, MD,[4,8] and Manish M. Sood, MD[1,2,4]

Background: The risk for venous thromboembolism (VTE) is elevated with albuminuria or a low estimated glomerular filtration rate (eGFR). However, the VTE risk due to the combined effects of eGFR and albuminuria are unknown.

Study Design: Population-based cohort study.

Settings & Participants: 694,956 adults in Ontario, Canada, from 2002 to 2012.

Factors: eGFR and albumin-creatinine ratio (ACR).

Outcome: VTE.

Results: 15,180 (2.2%) VTE events occurred during the study period. Both albuminuria and eGFR were independently associated with VTE. The association of albuminuria and VTE differed by level of eGFR (*P* for ACR × eGFR interaction < 0.001). After considering the competing risk for death, there was a 61% higher rate of VTE in patients with normal eGFRs (eGFRs > 90 mL/min/1.73 m^2) and heavy albuminuria (ACR > 300 mg/g) compared with those with normal eGFRs and no albuminuria (subdistribution HR, 1.61; 95% CI, 1.38-1.89). Among those with reduced kidney function (eGFR, 15-29 mL/min/1.73 m^2), the risk for VTE was only minimally increased, irrespective of albuminuria (subdistribution HRs of 1.23 [95% CI, 1-1.5] and 1.09 [95% CI, 0.82-1.45] for ACR < 30 and >300 mg/g, respectively).

Limitations: Only single determinations of ACR and eGFR were used. Diagnostic/*International Classification of Diseases* codes were used to define VTE.

Conclusions: Albuminuria increases the risk for VTE markedly in patients with normal eGFRs compared with those with lower eGFRs.

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INDEX WORDS: Venous thromboembolism (VTE); pulmonary embolism; deep vein thrombosis; chronic kidney disease (CKD); decreased kidney function; kidney failure; albuminuria; proteinuria; estimated glomerular filtration rate (eGFR); kidney function.

Venous thromboembolism (VTE) is recognized as a major health concern by the Surgeon General of the United States.[1] Chronic kidney disease (CKD) is a growing problem worldwide, with a prevalence of 10% to 15% in North America.[2-4] The definition and classification of CKD have undergone changes throughout the years with the recognition that albuminuria is an important risk factor for morbidity and mortality independent of kidney function. Currently, CKD is defined as abnormalities of kidney structure or function of more than 3 months' duration with implications for health. As such, the latest KDIGO (Kidney Disease: Improving Global Outcomes) CKD guideline from 2012 recommends that patients with CKD be risk classified according to both estimated glomerular filtration rate (eGFR) and albuminuria.[5]

Previous literature suggests an association with VTE and reduced kidney function or albuminuria[6-8]; however, results have been conflicting.[9,10] It remains unclear whether the higher VTE risk associated with albuminuria differs by level of kidney function. The long-term retention of uremic toxins or albuminuria alter many competing physiologic processes that may affect VTE risk, such as platelet function, the coagulation pathway, endothelial activity and inflammation, intravascular volume, and anemia

From the [1]Division of Nephrology, Department of Medicine, University of Ottawa; [2]Epidemiology, Ottawa Hospital Research Institute, Ottawa; [3]Division of Hematology, Department of Medicine, Western University, London, Ontario; [4]Institute for Clinical Evaluative Sciences, Toronto, Ontario; [5]Division of Nephrology, Department of Medicine, McMaster University, Hamilton, Ontario; and [6]Division of Nephrology, University of Alberta, Edmonton, Alberta; [7]Division of Nephrology, London Health Sciences Centre, Western University, London; and [8]Division of Nephrology, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada.

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Address correspondence to Manish M. Sood, MD, Ottawa Hospital Research Institute, The Ottawa Hospital, Civic campus, 2-014 Administrative Services Building, 1053 Carling Avenue, Box 693, Ottawa, Ontario, Canada K1Y 4E9. E-mail: msood@toh.on.ca

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with subsequent recombinant erythropoietin use. Furthermore, the CKD population is heterogeneous because a substantial proportion of patients present with isolated albuminuria (albumin-creatinine ratio [ACR] > 30 mg/g; 3.7%), isolated reductions in kidney function (eGFR < 60 mL/min/1.73 m^2; 2.2%), or both (1.4%).[11] An understanding of the individual and combined contributions of albuminuria and kidney function would aid in accurately determining VTE risk and targeting appropriate prophylactic therapies.

Given the prevalence of CKD in the population and the considerable biological alterations that it leads to, an understanding of the interplay of these risk factors warrants consideration. Using large population-based databases, we examined the association of VTE events in patients by albuminuria and eGFR.

METHODS

Design and Setting

Using health care databases housed at the Institute for Clinical Evaluative Sciences (ICES), we conducted a population-based retrospective cohort study in Ontario, Canada. The study protocol was approved by the Research Ethics Board at Sunnybrook Health Sciences Center in Toronto, Ontario, Canada. Patient consent was waived because the study used deidentified data. The reporting of this study follows the Reporting of Studies Conducted Using Observational Routinely Collected Data (RECORD) guidelines for observational studies.[12]

Data Sources

Patient characteristics, laboratory data, and outcome data were all obtained from linked databases in ICES. Both inpatient and outpatient data were retrieved. Outpatient laboratory data were obtained via the Cerner and Gamma-Dynacare databases. Cerner is a Health Information Technology provider that provides access to data from 11 hospitals in Southwestern Ontario. Gamma-Dynacare is a medical laboratory service that provides services such as outpatient blood work in more than 140 sites throughout Ontario. Demographics and diagnostics information were obtained through the Ontario Registered Persons Database, a registry of all inhabitants of Ontario who have an Ontario Health Insurance Plan, which is the free universal health care coverage for the province of Ontario containing all health care claims for both inpatient and outpatient services. The Canadian Institute for Health Information Discharge Abstract Database was also used to retrieve clinical diagnostic information from hospital admissions. The National Ambulatory Care Reporting System database contains diagnostic information from all emergency department visits. Information was also obtained from the Ontario Health Insurance Plan database, which contains all health claims for inpatient and outpatient physician services. We identified patients with a history of kidney transplantation using the Canadian Organ Replacement Register. These data sets were linked using unique encoded identifiers and analyzed at ICES. When possible, we defined patient characteristics and outcomes using validated codes (Table S1, available as online supplementary material).

Study Population

The mentioned databases were used to retrieve the study population. The study period ran from April 1, 2002, until March 31, 2012. Patients were included in the study if they had a urine ACR measurement and eGFR calculated within 12 months before the urine ACR measurement. The CKD-EPI (CKD Epidemiology Collaboration) creatinine equation was used to calculate eGFR.[13] The date of the urine ACR measurement was counted as the index date for study inclusion. ACR and eGFR are outpatient values that have been previously validated.[14] Serum creatinine values were corrected for isotope-dilution mass spectrometry harmonization. Patients were excluded if there were missing data (age and sex), were non-Ontario residents, were younger than 40 years, had end-stage renal disease (ESRD; defined as eGFR < 15 mL/min/1.73 m^2 [small number of patients], long-term dialysis therapy, or kidney transplantation), or had a documented VTE event before the index date (look back until 1981).

Study Groups and Outcomes

The main exposure of interest was albuminuria using ACR. Various baseline characteristics of patients, including sex, age, demographics, and comorbid conditions, were retrieved using the previously described databases and compared between the different groups of eGFR and urine ACR.

We used the Adjusted Clinical Group scoring system to score comorbid conditions.[15] The Adjusted Clinical Group is a population/patient case-mix adjustment system that provides a relative measure of the individual's expected consumption of health services. The *International Classification of Diseases, Ninth Revision* (*ICD-9*)/*ICD-9, Clinical Modification* (*ICD-9-CM*) codes are categorized into 32 groups, called ambulatory diagnostic groups, on the basis of clinical similarity, chronicity, likelihood of requiring specialty care, and disability. These groups are further reduced to 12 collapsed ambulatory diagnostic groups.

The study outcome was the first event of documented VTE. These events were captured using a validated algorithm for a diagnosis of deep vein thrombosis or pulmonary embolism that combines *ICD* codes with diagnostic imaging billing codes (sensitivity, 75%; specificity, 93.8%).[16] Patients were followed up until the time of VTE event, ESRD (in this case defined as long-term dialysis therapy or kidney transplantation), death, or end of study period (March 31, 2012). Although ESRD (because the risk for VTE changes considerably after ESRD) and end of study period were considered as censoring events, death was considered as a competing event. Because pulmonary embolism may be a fatal event, the additional composite outcome of death or VTE was also examined.[17,18]

Statistical Analysis

Differences in baseline characteristics among albuminuria categories were calculated using Cochrane-Armitage tests for categorical variables and 1-way analysis of variance with a linear contrast or Jonckheere trend test for continuous variables. Patients were divided into groups based on kidney function and ACR as per KDIGO recommendations for classifying CKD. For kidney function, patients were categorized according to GFR categories; that is, stage 1: eGFR ≥ 90 mL/min/1.73 m^2 (group G1); stage 2: 60 to 89 mL/min/1.73 m^2 (group G2); stage 3a: 45 to 59 mL/min/1.73 m^2 (group G3a); stage 3b: 30 to 44 mL/min/1.73 m^2 (group G3b); and stage 4: 15 to 29 mL/min/1.73 m^2 (group G4). For albuminuria, patients were categorized according to albuminuria categories; that is, ACR < 30 mg/g (<3 mg/mmol; group A1); ACR of 30 to 300 mg/g (3-30 mg/mmol; group A2); and ACR > 300 mg/g (>30 mg/mmol; group A3). To avoid the influence of extreme outliers of ACR, we truncated maximum values at 500 mg/g. There were 14,805 observations (2.13% of total ACR) > 500 mg/g that were set to 500 mg/g. In sensitivity analysis, all ACRs were included and models were repeated. The crude number and percentage of VTE events were calculated for each different category of ACR and kidney function. In the

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