Vascular complications in kidney disease

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Chapter 3

Chronic kidney disease stage 1-3 increases risk of venous thrombosis

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ABSTRACT

Background: End-stage renal disease has been associated with venous thrombosis (VT). However, the risk of VT in early stages of chronic kidney disease (CKD) has not yet been investigated. The aim of this study was to investigate whether CKD patients with stage 1-3 are at increased risk of VT.

Methods: 8 495 subjects were included in a prospective cohort study, in which renal function and albuminuria was assessed, starting in 1997-1998, and were followed for the occurrence of VT until 1 June 2007. CKD patients were staged according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, on the basis of 24-h urine albumin excretion and estimated glomerular filtration rates. Objectively verified symptomatic VT was considered as endpoint.

Results: Of the 8 495 subjects, 243 had CKD stage 1, 856 CKD stage 2, and 491 CKD stage 3. During a median follow-up period of 9.2 years, 128 individuals developed VT. The hazard ratios (HRs) for CKD stages 1, 2, and 3 were, respectively, 2.2 (95% CI 0.9-5.1), 1.9 (95% CI 1.1-3.1), and 1.6 (95% CI 0.9-2.8) relative to those without CKD after adjustment for age, sex, BMI, hypertension, diabetes, malignancy, and high-sensitivity C-reactive protein. Subjects with CKD stage 3 and albuminuria (≥30 mg per day) had an adjusted HR of 3.0 and subjects with stage 3 without albuminuria had an adjusted HR of 1.0.

Conclusion: CKD stages 1 and 2, and CKD stage 3 in presence of albuminuria are risk factors for VT. The risk of VT is more related to albuminuria than to impaired glomerular filtration rate.

INTRODUCTION

Patients with severe chronic kidney disease (CKD) have increased risks of both arterial cardiovascular disease as well as for venous thrombosis (VT). The Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines defined CKD as either kidney damage (albuminuria ≥30 mg per day) or decreased kidney function and categorized CKD in five stages.[1,2] The prevalence of CKD in the US is now 13% and is increasing, predominantly as a result of the type II diabetes epidemic.[3]

The increased risk of arterial cardiovascular disease in CKD has been known for a long time and has been studied extensively for different CKD stages.[4-8] Recent studies have also shown an association between overt CKD and VT.[9,10] A study of the PREVEND cohort showed that the presence of micro-albuminuria (albuminuria 30-300 mg per day) was a risk factor for VT.[9] Another study of the LITE cohort showed that patients with estimated glomerular filtration rates (eGFR) between 15 and 60 ml/min (CKD stage 3-4) had a two-fold increased risk of VT as compared to subjects with a normal kidney function (eGFR >90 ml/min).[10] However, information on albuminuria was not available in this study. To our knowledge, there is no study on the risk of VT in the different CKD stages taking into account albuminuria which is a prerequisite for staging CKD and for defining patients without CKD.

Therefore, we investigated whether patients with CKD stage 1, 2, and 3 had an increased risk of VT in a large population-based cohort, and set out to determine absolute and relative risks for various stages of CKD.

METHODS

Study population and design

For this study, we used data of PREVEND study, which was designed to investigate the association between albuminuria and renal and cardiovascular outcomes in the general population. Details of the study have been published elsewhere[11-13] and can be found at http://www.prevend.org. The study outline is presented in Figure 1. In summary, all inhabitants of the city of Groningen, the Netherlands, aged 28-75 years (n= 85 421) were invited to send a morning urine sample to screen for albuminuria. Of these subjects, 40 856 responded. From these responders, the PREVEND cohort was selected aiming for a cohort enriched for the presence of albuminuria. Pregnant women and subjects with insulin-dependent diabetes mellitus were excluded. All participants with an urinary albumin concentration (UAC) of ≥10 mg/L were invited (N=9 966), of whom 6 000 subjects participated. Furthermore, a randomly selected cohort group of

2 592 subjects selected from 30 890 respondents with UAC of <10 mg/L participated. These 8 592 subjects formed the baseline PREVEND cohort. These participants twice visited an outpatient clinic for measurements concerning their health. For the current study, subjects were excluded because of missing data on 24-h urinary albumin excretion or creatinine (n=86). Furthermore, subjects with CKD stage 4 (n=8) or stage 5 (n=3) were excluded, one of whom had a VT event, leaving 8 495 subjects for the present analysis. The PREVEND study has been approved by the local medical ethics committee and is conducted in accordance with the guidelines of the Declaration of Helsinki.

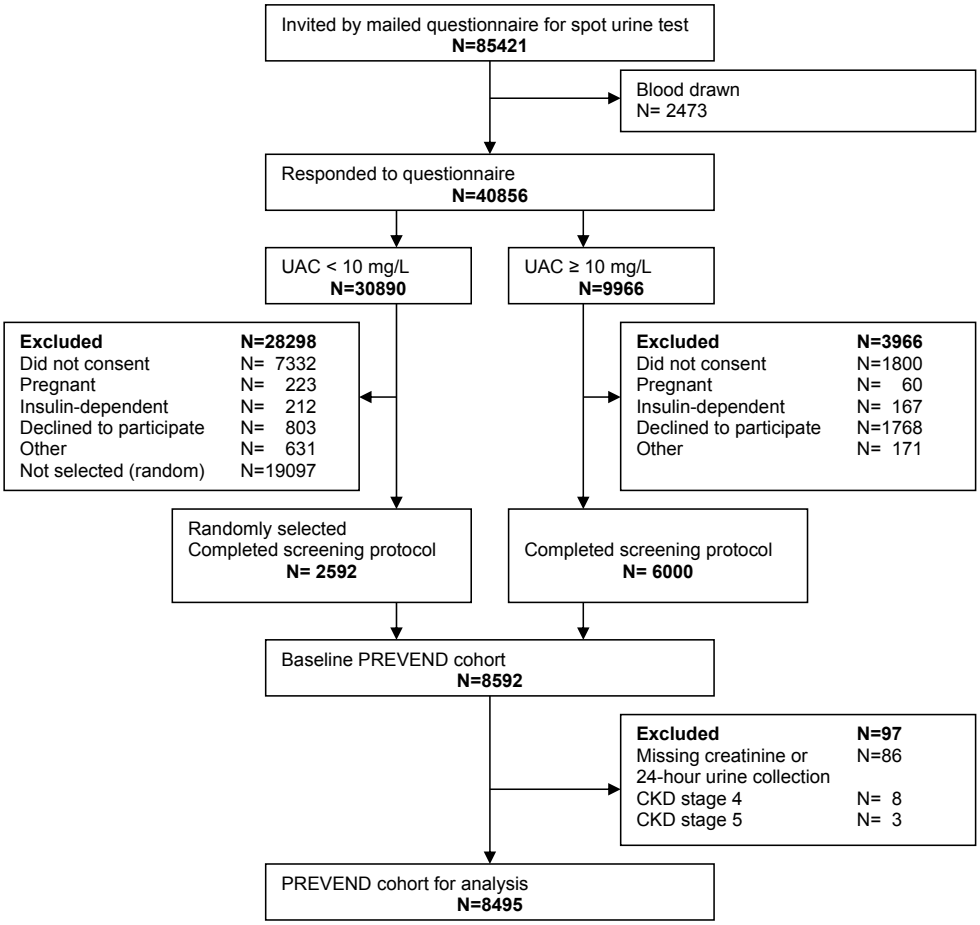

Figure 1. Outline of the PREVEND study
CKD, chronic kidney disease; UAC, urinary albumin concentration

Measurements and definitions

Serum creatinine, total cholesterol, and plasma glucose were measured by dry chemistry (Eastman Kodak, Rochester, New York). The high-sensitivity C-reactive protein (hsCRP) level was determined by nephelometry (BN II, Dade Behring, Marburg, Germany). Participants collected two 24-h urine samples, in which UAC was determined by nephelometry (BN II, Dade Behring, Marburg, Germany). The amount of albuminuria was measured as the mean of the two 24-hour urine samples.

Hypertension was defined as systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, or the use of antihypertensive drugs. Diabetes was defined as a fasting glucose level of ≥126 mg/dL, a non-fasting plasma glucose levels of ≥200 mg/dL, or the use of oral antidiabetic drugs. Hypercholesterolemia was defined as a total serum cholesterol concentration ≥250 mg/dL, or in case of a previous myocardial infarction or stroke a concentration of ≥193 mg/dL, or the use of lipid-lowering drugs. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. GFR was estimated by the Modification of Diet in Renal Disease (MDRD) study equation[14] taking into account sex, age, race, and serum creatinine level. In an additional analysis, the newly developed but less often used Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study equation[15] was used to estimate eGFR to compare these results with the results of the MDRD-equation. The CKD-EPI equation has been shown to outperform the MDRD equation in estimating the GFR above the 60 ml/min.[15]

Chronic kidney disease

CKD was staged according to the K/DOQI guidelines.[1,2] CKD stage 1 was defined as eGFR >90 ml/min and albuminuria (urinary albumin excretion ≥30 mg per 24-hour urine collection), CKD stage 2 as eGFR between 60 and 90 ml/min and albuminuria, and CKD stage 3 as eGFR between 30 and 60 ml/min.

Venous thrombosis

The regional anticoagulation clinic database was used to identify participants who developed VT between January 1997 and June 2007. In the Netherlands, all outpatient treatment with vitamin K antagonists is monitored by regional anticoagulation clinics. Therefore, all VT events in treated outpatients are recorded by anticoagulation clinics. Moreover, as a secondary check for outpatient VT cases and identification of within hospital (fatal) cases, all study participants were searched for VT events in the national registry of death certificates and the national registry of hospital discharge diagnoses datasets. With the use of three independent sources, it is unlikely that VT events will be missed. The investigators who collected these data were blinded for CKD stages of the participants. In addition, all VT events according

to the three sources were validated by reviewing medical records of these patients. Only objectively verified symptomatic VT events were considered. Deep vein thrombosis (DVT) was confirmed by compression ultrasound and pulmonary embolism (PE) by ventilation-perfusion lung scanning, spiral computed tomography, or at autopsy. The observation time of each participant was calculated as a time elapsed between the testing of albuminuria (1997-1998) and the first episode of VT or a censoring event (withdrawal from the study, moving out of the city, death, or June 2007), whichever occurred first. Incidence rates for VT were calculated by dividing the number of patients with a VT by the total observation time at risk. VT was considered to be unprovoked in the absence of major surgery, trauma, immobilization for >7 days, oral contraceptives, hormone therapy, pregnancy, malignant disease, long-distance travel for >4 hours, active infectious disease, paresis/paralysis of the leg, or heart failure at or within three months before the development of VT. Medical records were viewed with a checklist including these well-defined and well-documented variables to categorize VT into provoked or unprovoked.

Statistical analyses

Baseline characteristics of the participants were compared between subjects without CKD and subjects with CKD stages 1-3. Continuous data were reported as medians with interquartile ranges. Kaplan-Meier life-tables were used to estimate cumulative survival for CKD stages 1-3 and no CKD. To investigate whether patients with CKD stages 1-3 had an increased risk of VT, proportional hazard regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) as compared to participants without CKD (reference group). All analyses were performed for CKD stages 1, 2, and 3 combined and separately. In contrast to CKD stages 1 and 2, CKD stage 3 is only defined by decreased eGFR (between 30 and 60 ml/min) and not by the presence of albuminuria, according to the K/DOQI guidelines. We also calculated HRs for CKD stage 3 stratified for the presence of albuminuria. We adjusted the HRs for age, sex, and BMI and additional for hypertension, diabetes, malignancy, and hsCRP. HRs were not adjusted for other cardiovascular risk factors such as hyperlipidemia and smoking, since these were not associated with VT in the PREVEND cohort.[9] We repeated the same analyses for provoked and unprovoked VT separately.

To investigate whether eGFR is a risk factor for VT apart from albuminuria, we calculated HRs with 95% CIs for eGFR adjusted for albuminuria and for albuminuria adjusted for eGFR to evaluate the associations of level of eGFR and albuminuria with risk of VT. Furthermore, we divided subjects in six categories based on albuminuria and eGFR (>90 ml/min, between 60 and 90 ml/min, and between 30 and 60 ml/min). HRs with 95% CIs were calculated for eGFR in absence or presence of albuminuria as compared with subjects with eGFR >90 ml/min without albuminuria (reference group).

Finally, we calculated HRs with 95% CIs for CKD stages 1-3 as compared to participants without CKD, using the CKD-EPI formula for staging CKD. STATA software version 10.1 (StataCorp LP, College Station, Tx) was used for the statistical analyses.

RESULTS

The baseline characteristics of the 8 495 subjects are shown in Table 1. Of the 6 905 subjects without CKD, 26.4% had an eGFR >90 ml/min and 73.6% had an eGFR between 60 and 90 ml/min. Of the 1 590 with CKD, 243 were in stage 1, 856 in stage 2, and 491 in stage 3. Of the 491 subjects with stage 3 CKD, 164 had albuminuria (≥30 mg per day). Subjects with CKD stages 1-3 were older, were more often male, more often had diabetes, hypertension and malignancy, and had a higher BMI and higher CRP levels than subjects without CKD. The age of CKD patients increased with the CKD stage.

Overall, 128 subjects developed VT during a median observation period of 9.2 years (ranging from 0 to 10 years). Of the 128 patients with VT, 72 (56%) had DVT only, 44 had PE only (34%), and 12 (9%) had a combination of both. Of the 1590 subjects with CKD stage 1-3, 49 developed VT as compared with 79 of the 6905 subjects without CKD. Seven of the 243 patients with CKD stage 1, 26 of the 856 patients with CKD stage 2, and sixteen of 491 patients with CKD stage 3 developed VT. Four patients died because of a PE (three in CKD stage 3 and one without CKD). Furthermore, there was no significant difference in the distribution of PE and DVT in CKD stage 3 (63% of VT patients had a PE) as compared to CKD stages 1 and 2 (36% had a PE) (P=0.09) or as compared to no CKD (43% had a PE) (P=0.16). The cumulative incidences for VT at eight years of follow-up were 3.2% for CKD stage 1, 3.0% for stage CKD 2, 3.3% for CKD stage 3, 3.1% for CKD stages 1-3, and 1.1% for no CKD. The number needed to treat to prevent one VT event in patients with CKD stage 1-3 was approximately 400 patients per year. Figure 2 shows the Kaplan-Meier risk curves for VT events for patients with CKD stage 1-3 versus subjects without CKD.

Table 1. Baseline characteristics

Characteristic	No CKD (n=6905)	CKD stage 1-3 (n=1590)	CKD stage 1 (n=243)	CKD stage 2 (n=856)	CKD stage 3 (n=491)
Age* (years)	46 (37-56)	59 (48-67)	47 (39-56)	58 (48-66)	65 (58-70)
Male, %	49	56	66	64	38
Caucasians, %	95	96	93	97	97
Diabetes, %	2.4	9.8	12.8	11.2	5.9
Hypertension, %	27	65	50	65	72
Hypercholesterolemia, %	28	46	36	44	54
BMI* (kg/m^2)	25 (23-28)	27 (24-30)	27 (24-30)	27 (25-30)	27 (25-30)
hsCRP* (mg/L)	1.1 (0.5-2.7)	2.2 (1.0-4.6)	2.1 (0.9-4.9)	2.3 (1.0-4.4)	2.2 (1.1-4.8)
Malignancy, %	1.4	2.3	1.6	2.2	2.8
eGFR* (ml/min)	81 (73-91)	72 (59-83)	97 (93-104)	76 (69-82)	55 (51-58)
UAE* (mg per day)	8 (6-12)	47 (33-93)	57 (39-101)	59 (39-107)	14 (7-47)

CKD, chronic kidney disease; BMI, body mass index; hsCRP, high-sensitivity c-reactive protein; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion. *median (interquartile range)

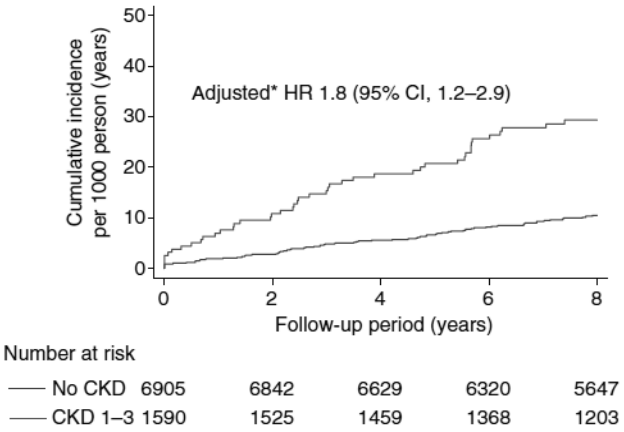

Figure 2. **Kaplan-Meier estimates of the risk of venous thrombosis according to stages of chronic kidney disease**
CKD, chronic kidney disease; prs-yrs, person-years; yrs, years. *Adjusted for age, sex, body mass index, hypertension, diabetes, malignancy, and hsCRP

The incidence rate for VT in subjects without CKD was 1.3 (95% CI 1.1-1.7) per 1000 person-years and 3.7 (95% CI 2.8-4.0) for subjects with CKD stages 1-3 with a corresponding HR for VT of 2.8 (95% CI 2.0-7.3) for CKD stages 1-3 as compared with no CKD. The HR decreased to 1.8 (95% CI 1.2 -2.9) after adjustment for age, sex, BMI, hypertension, diabetes, malignancy, and hsCRP.

The crude HRs were 2.6 (95% CI 1.2-5.6), 2.8 (95% CI 1.8-4.3), and 3.0 (95% CI 1.8-5.2) for respectively CKD stages 1, 2, and 3. Figure 3 shows adjusted HRs with 95% CIs for CKD stages 1, 2, and 3, the last with or without the presence of albuminuria as compared with no CKD. The HRs were 2.2 (95% CI 0.9 -5.1), 1.9 (95% CI 1.1 -3.1), and 1.6 (95% CI 0.9 -2.8). For CKD stage 3 with and without albuminuria, the HRs were, respectively, 5.5 (95% CI 2.8-11.0) and 1.9 (95% CI 0.9-4.2) without adjustment, and 3.0 (95% CI 1.4-6.5) and 1.0 (95% CI 0.4-2.4) after full adjustment.

Of the 128 VT events, 66 were unprovoked (51.6%) and 62 (48.4%) were provoked (Table 2). For unprovoked VT, the HRs after adjustment for age, sex, BMI, hypertension, diabetes, malignancy, and hsCRP were 2.1 (95% CI 1.2-3.6) for CKD stages 1-3, 2.5 (95% CI 0.8-7.4) for CKD stage 1, 2.4 (95% CI 1.3-4.4) for CKD stage 2, and 1.4 (95% CI 0.6-3.3) for CKD stage 3. For provoked VT, the HRs after adjustment were 1.2 (95% CI 0.6-2.3) for CKD stages 1-3, 1.4 (95% CI 0.3-5.9) for CKD stage 1, 0.8 (95% CI 0.3-2.2) for CKD stage 2, and 1.7 (95% CI 0.8-3.9) for CKD stage 3.

Albuminuria was associated with a 2.1-fold increased risk of VT after adjustment for age, sex, BMI, hypertension, diabetes, malignancy, hsCRP, and eGFR (Table 3). As compared with subjects with an eGFR >90 ml/min, subjects with an eGFR between 30 and 60 ml/min had 50% increased risk of VT after adjustment for after adjustment for age, sex, BMI, hypertension, diabetes, malignancy, hsCRP, and albuminuria.

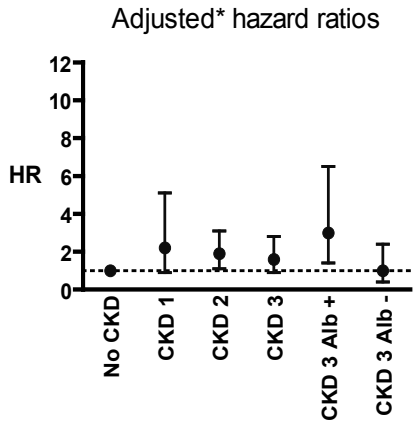

Figure 3. Adjusted hazard ratios for venous thrombosis by CKD stage
CKD, chronic kidney disease; HR, hazard ratio; eGFR, estimated glomerular filtration rate; CKD 3 Alb +, CKD stage 3 and urinary albumin excretion ≥30 mg per day; CKD 3 Alb -, CKD stage 3 and urinary albumin excretion <30 mg per day. *Adjusted for age, sex, body mass index, hypertension, diabetes, malignancy, and hsCRP

Table 2. Incidence rates and hazard ratios for provoked and unprovoked venous thrombosis

	No CKD (n=6905)	CKD stage 1-3 (n=1590)	CKD stage 1 (n=243)	CKD stage 2 (n=856)	CKD stage 3 (n=491)
Unprovoked venous thrombosis					
No. of venous thrombosis	35	31	5	19	7
Incidence rate per 1000 person-years	0.6 (0.4-0.8)	2.4 (1.7-3.4)	2.5 (1.0-5.9)	2.7 (1.7-4.2)	1.7 (0.8-3.7)
Crude hazard ratios (95% CI)	1.0	4.0 (2.5-6.5)	4.2 (1.6-10.6)	4.5 (2.6-7.9)	3.0 (1.3-6.7)
Adjusted* hazard ratios (95% CI)	1.0	2.1 (1.5-3.5)	3.0 (1.1-.8.0)	2.3 (1.3-4.2)	1.4 (0.6-3.2)
Adjusted† hazard ratios (95% CI)	1.0	2.1 (1.2-3.6)	2.5 (0.8-.7.4)	2.4 (1.3-4.4)	1.4 (0.6-3.3)
Provoked venous thrombosis					
No. of venous thrombosis	44	18	2	7	9
Incidence rate per 1000 person-years	0.7 (0.5-1.0)	1.4 (0.9-2.2)	1.0 (0.2-3.9)	1.0 (0.5-2.1)	2.3 (1.2-4.4)
Crude hazard ratios (95% CI)	1.0	1.9 (1.1-3.2)	1.3 (0.3-5.5)	1.3 (0.6-3.0)	3.1 (1.5-6.3)
Adjusted* hazard ratios (95% CI)	1.0	1.2 (0.7-2.2)	1.2 (0.3-4.9)	1.0 (0.4-2.2)	1.7 (0.8-3.6)
Adjusted† hazard ratios (95% CI)	1.0	1.2 (0.6-2.3)	1.4 (0.3-5.9)	0.8 (0.3-2.2)	1.7 (0.8-3.9)

CKD, chronic kidney disease. *Adjusted for age, sex, and body mass index. †Adjusted for age, sex, body mass index, hypertension, diabetes, malignancy, and hsCRP

Table 4 shows HRs for VT for decreased eGFR (between 60 and 90 ml/min and between 30 and 60 ml/min) in absence and presence of albuminuria as compared with subjects with eGFR >90ml/min without albuminuria. The adjusted HRs for subjects without albuminuria and an eGFR between 60 and 90 ml/min or an eGFR between 30 and 60 ml/min were, respectively, 1.5 (95% CI 0.7-3.1) and 1.4 (95% CI 0.5-4.1). HRs for VT were increased in the presence of albuminuria in all eGFR categories. The adjusted HRs were 3.1 (95% CI 1.1-8.9), 2.7 (95% CI 1.2-6.1), and 4.1 (95% CI 1.5-11.0) for subjects with albuminuria and, respectively, eGFR >90 ml/min, eGFR between 60 and 90 ml/min, and eGFR between 30 and 60 ml/min.

The HRs for VT in CKD stages 1, 2, and 3 were, respectively, 1.6 (95% CI, 0.7-3.8), 1.9 (95% CI, 1.2-3.0), and 1.5 (95% CI, 0.9-2.7) using the CKD-EPI formula after adjustment for age, sex, and BMI. HRs for subjects with CKD stage 3 and albuminuria and subjects with CKD stage 3 without albuminuria were, respectively, 1.9 (95% CI 0.9-4.1) and 1.3 (95% CI 0.6-2.8) after adjustment.

Table 3. Association between eGFR, albuminuria, and risk for venous thrombosis

	Adjusted* hazard ratios
eGFR	
> 90 ml/min	1.0 (reference)
60-90 ml/min	1.3 (0.7-2.3)
30-60 ml/min	1.5 (0.7-3.3)
	Adjusted† hazard ratios
Albuminuria‡	
No	1.0 (reference)
Yes	2.1 (1.4-3.2)

eGFR, estimated glomerular filtration rate. *Adjusted for age, sex, body mass index, hypertension, diabetes, malignancy, and hsCRP, and albuminuria (continuous). †Adjusted for age, sex, body mass index, hypertension, diabetes, malignancy, and hsCRP, and eGFR (continuous). ‡Albuminuria defined as urinary albumin excretion ≥30 mg per day

Table 4. Hazard ratios for venous thrombosis by decreased glomerular filtration rates and albuminuria

			Crude hazard ratios		Adjusted* hazard ratios	
			No albuminuria	Albuminuria†	No albuminuria	Albuminuria†
eGFR > 90 ml/min		HR (95% CI)	1.0 (reference)	4.8 (1.9-12.4)	1.0 (reference)	3.1 (1.1-8.9)
eGFR	60-90 ml/min	HR (95% CI)	2.2 (1.2-4.1)	5.2 (2.6-10.5)	1.5 (0.7-3.1)	2.7 (1.2-6.1)
eGFR	30-60 ml/min	HR (95% CI)	3.6 (1.4-9.3)	10.3 (4.2-24.7)	1.4 (0.5-4.1)	4.1 (1.5-11.0)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion per day. *Adjusted for age, sex, body mass index, hypertension, diabetes, malignancy, and hsCRP. †Albuminuria defined as urinary albumin excretion ≥30 mg per day

DISCUSSION

In this study including 8 495 subjects followed for over 8 years, we found a 2.2-fold (95% CI 0.9 -5.1) increased risk of VT in patients with CKD stage 1 and a 1.9-fold (95% CI 1.1 -3.1) increased risk of VT in patients with CKD stage 2 as compared with subjects without CKD according to the K/DOQI guidelines. CKD stage 3 patients with albuminuria had 3.0-fold (95% CI 1.4-6.5) increased risk of VT, and CKD stage 3 patients without albuminuria had a HR of 1.0 (95% CI 0.4-2.4). The risk of VT associated with CKD seemed to be related to albuminuria rather than to impaired eGFR. Furthermore, our findings showed that CKD stages 1-3 were mainly associated with unprovoked VT. Using the CKD-EPI formula instead of the MDRD formula for staging CKD did not result in large differences for any of the analyses.

Previous studies have investigated the association between eGFR on the basis of MDRD and VT.[10,16] In the study of the LITE cohort, HRs for VT were 1.3 (95% CI 1.0-1.6) for subjects with eGFR between 60 and 90 ml/min and 2.1 (95% CI 1.5-3.0) for subjects with eGFR between 15 and 60 ml/min (CKD stage 3-4) as compared with subjects with eGFR >90 ml/min.[10] However, information on albuminuria was not available in this study and formal classification into CKD stages was therefore not possible. In our study, we found a HR of 1.5 for VT for CKD stage 3 after adjustment for age, sex, and BMI; we showed that the risk of VT was only increased in the presence of albuminuria. Recent findings from the LITE study group contrast their earlier findings: eGFR based on cystatin was associated with an approximately 1.6-fold increased risk of VTE, while eGFR based on creatinine was not associated with an increased risk of VT.[16] The authors could not explain the discrepancy between the earlier and the current finding. Furthermore, albuminuria was not a risk factor for VT in their study, in contrast to our study. An explanation for this discrepancy could be that the relatively low prevalence of albuminuria may have limited their power to detect an association between VT and albuminuria, whereas our cohort was enriched for the presence of albuminuria. Moreover, in our study albuminuria was assessed in 24-h urine samples (gold standard) that were not frozen before assessment, whereas in their study albuminuria was assessed by albumin-creatinine ratio in frozen samples. Frozen storage is known to induce a systematic decrease and more variability in albuminuria concentration.[17] Furthermore, subjects with albuminuria are probably mainly diabetics in their study, while in PREVEND these are mainly non-diabetics, as per protocol insulin-using diabetic patients were excluded. This may have influenced the risk estimates, as diabetic subjects are usually on statin therapy and more frequently treated with anti-platelet medication for their cardiovascular morbidity. New findings indicate that statin use may reduce the risk of VT.[18]

Although the seemingly higher risk of VT in CKD stages 1 and 2 as compared with stage 3 might be surprising, the same pattern in the association between CKD and cardiovascular disease was previously found in the PREVEND study.[4] Patients with CKD stages 1 and 2 were at higher risk of cardiovascular disease than those with CKD stage 3. A plausible explanation for this might be the difference in staging of CKD stage 3 and CKD stages 1 and 2. Albuminuria is necessary to define CKD stages 1 and 2, whereas only GFR is needed to define CKD stage 3 to 5. Therefore, CKD stage 3 is a heterogeneous category, with subjects with and without evident kidney damage (albuminuria). We found that CKD stage 3 patients with albuminuria were at higher risk of VT than CKD stage 3 patients without albuminuria. These findings are in line with several other studies suggesting a higher risk for CKD stage 3 subjects with albuminuria than for CKD stage 3 subjects without albuminuria for different adverse outcomes, such as cardiovascular disease and the development of end-stage renal disease.[19-21] Taken together, these data suggest that information on albuminuria could be added to CKD stage 3 in order to improve the value of CKD staging for risk prognosis.

There are several possible mechanisms for the increased risk of VT in CKD. First, endothelial damage could explain the increased risk of VT. It is remarkable that the association between CKD stages 1-3 and VT was comparable with the previously reported association between CKD stages 1-3 and cardiovascular disease in the PREVEND study.[4] Therefore, it is tempting to hypothesize that a common risk factor for CKD leads to both VT and arterial cardiovascular disease. In our analysis, hypertension, BMI, and diabetes did not explain the increased risk of VT. Second, the increased risk of VT could be attributable to procoagulant changes in CKD patients which may be predominantly present in subgroups of CKD patients such as patients with nephrotic syndrome.[22] CKD and nephrotic syndrome have been associated with elevated levels of D-dimer, CRP, fibrinogen, factor VII, factor VIII, and von Willebrand factor,[23,24] which are important proteins in the development of VT. Third, inflammation may explain the increased risk of VT in CKD. It has been suggested that inflammation leads to VT.[25] However, additional adjustment of the HRs for hsCRP, which is currently the most widely used biomarker of inflammation,[26] did not alter the HRs in our study.

This study has several limitations. First, the K/DOQI guidelines require impaired GFR or albuminuria for at least three months. As in most studies, repeated measurements for a period of at least three months were not available in our study, and some subjects may therefore have been falsely classified as having CKD. Second, VT events were identified through anticoagulation clinic databases and registries for hospital discharge diagnoses and death certificates, which could lead to an underestimation of the incidence rates of VT. However, the incidence rates for VT in the PREVEND cohort (i.e. 1.4 per 1000 person-years) correspond well to those found in studies that had a complete case-finding procedure of objectively confirmed VT events.[27] Third, we may have underestimated renal function in subjects with a GFR >60 ml/min, because we used the MDRD study equation.[28,29] However, use of the CKD-EPI formula did not result in large differences in the HRs. Fourth, there are studies suggesting that risk of adverse events increases when GFR drops below 45 ml/min.[7,20] Our study did not include enough subjects with an eGFR <45 ml/min (n=52) to investigate this. Despite these limitations, PREVEND is a unique cohort in its large population-based prospective setting in which albuminuria was assessed in two 24-h urine samples.

We showed that CKD stages 1, 2, and 3 in the presence of albuminuria are risk factors for VT. The relative risk of VT for those with CKD stage 1-3 was 1.8-fold increased relative to those without CKD. Although these relative risk estimates may be considered to be weak as compared with, for example, relative risk estimates for venous thrombosis that have been reported for genetic thrombophilia,[30] on a population level CKD may be an important contributor to VT, because of the high prevalence of CKD, i.e. 12.7% for CKD stages 1-3 in the general population.[3] This is greater than most well-known genetic risk factors for VT, such as

prothrombin gene mutation.[31] Clinicians should be aware of the increased risk of VT in these patients. Further studies are needed to show whether VT prophylaxis in subgroups of these patients will be safe and cost-effective, especially as the high risk of anticoagulant treatment-related major bleeding episodes applies to CKD stage 4 and 5, and not CKD stage 1-3.[32]

In conclusion, CKD stages 1 and 2, and CKD stage 3 in presence of albuminuria were risk factors for VT. The risk of VT is more related to albuminuria than to impaired eGFR.

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