Thromboembolic disease of the venous and the arterial system
Mahmoodi, Bakhtawar Khan

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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 June 1, 2007. CKD patients were staged according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines based on 24-hour urine albumin excretions and estimated glomerular filtration rates (GFR). Objectively verified symptomatic VT was considered as endpoint.

Results: Of the 8,495 subjects, 243 had stage 1 CKD, 856 stage 2, and 491 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 hsCRP. 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.

Conclusions: CKD stage 1, 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 GFR.
Introduction

Patients with severe chronic kidney disease (CKD) have both an increased risk of 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 a glomerular filtration rate (GFR) 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 (GFR >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 design and population
For this study, we used data of the Prevention of Renal and Vascular Disease (PREVEND) study. The PREVEND study 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-hour urinary albumin excretion or creatinine (n=86). Furthermore, subjects with CKD stage 4 (n=8) or stage 5 (n=3) were excluded of whom one 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.

Measurements and definitions
Serum creatinine, total cholesterol, and plasma glucose were measured by dry chemistry (Eastman Kodak, Rochester, New York). High-sensitivity C-reactive protein (hsCRP) was determined by nephelometry (BN II, Dade Behring, Marburg, Germany). Participants collected two 24-hour 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.
Chapter 4

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

Hypertension was defined as systolic blood pressure of $\geq 140$ mm Hg, diastolic blood pressure of $\geq 90$ mm Hg, or the use of antihypertensive drugs. Diabetes was defined as a fasting glucose level of $\geq 126$ mg/dL, nonfasting plasma glucose levels of $\geq 200$ mg/dL, or the use of oral antidiabetic drugs. Hypercholesterolemia was defined as a total serum cholesterol concentration $\geq 250$ mg/dL, or in case of a previous myocardial infarction or stroke a concentration of $\geq 193$ 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 eGFR 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 to miss VT events. 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 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 check-list 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 stage 1-3. Continuous data were reported as medians with interquartile ranges. Kaplan-Meier life-tables were used to estimate cumulative survival for CKD stage 1-3 and no CKD. To investigate whether patients with CKD stage 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 stage 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 to 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 a GFR >90 ml/min and 73.6% had a GFR 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 stage 1-3 were older, were more often male, had more often diabetes, hypertension and malignancy, and had a higher body mass index and higher CRP levels than subjects without CKD. The age of CKD patients increased with the CKD stage.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No CKD (n=6905)</th>
<th>CKD stage 1-3 (n=1590)</th>
<th>CKD stage 1 (n=243)</th>
<th>CKD stage 2 (n=856)</th>
<th>CKD stage 3 (n=491)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age* (years)</td>
<td>46 (37-56)</td>
<td>59 (48-67)</td>
<td>47 (39-56)</td>
<td>58 (48-66)</td>
<td>65 (58-70)</td>
</tr>
<tr>
<td>Male, %</td>
<td>49</td>
<td>56</td>
<td>66</td>
<td>64</td>
<td>38</td>
</tr>
<tr>
<td>Caucasians, %</td>
<td>95</td>
<td>96</td>
<td>93</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>2.4</td>
<td>9.8</td>
<td>12.8</td>
<td>11.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>27</td>
<td>65</td>
<td>50</td>
<td>65</td>
<td>72</td>
</tr>
<tr>
<td>Hypercholesterolemia,%</td>
<td>28</td>
<td>46</td>
<td>36</td>
<td>44</td>
<td>54</td>
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<tr>
<td>BMI* (kg/m²)</td>
<td>25 (23-28)</td>
<td>27 (24-30)</td>
<td>27 (24-30)</td>
<td>27 (25-30)</td>
<td>27 (25-30)</td>
</tr>
<tr>
<td>hsCRP* (mg/L)</td>
<td>1.1 (0.5-0.7)</td>
<td>2.2 (1.0-4.6)</td>
<td>2.1 (0.9-4.9)</td>
<td>2.3 (1.0-4.4)</td>
<td>2.2 (1.1-4.8)</td>
</tr>
<tr>
<td>Malignancy, %</td>
<td>1.4</td>
<td>2.3</td>
<td>1.6</td>
<td>2.2</td>
<td>2.8</td>
</tr>
<tr>
<td>eGFR* (ml/min)</td>
<td>81 (73-91)</td>
<td>72 (59-83)</td>
<td>97 (93-104)</td>
<td>76 (69-82)</td>
<td>55 (51-58)</td>
</tr>
<tr>
<td>UAE* (mg per day)</td>
<td>8 (6-12)</td>
<td>47 (33-93)</td>
<td>57 (39-101)</td>
<td>59 (39-107)</td>
<td>14 (7-47)</td>
</tr>
</tbody>
</table>

Table 1. Baseline characteristics

CKD indicates 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)

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 1,590 subjects with CKD stage 1-3, 49 developed VT as compared with 79 of the 6,905 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 stage 1-2 (36% had a PE) (P=0.09) or as compared to no CKD (43% had a PE) (P=0.16). The cumulative incidence for VT at eight years of follow-up were 3.2% for CKD stage 1, 3.0% for stage 2, 3.3% for stage 3, 3.1% for stage 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.

![Kaplan-Meier curves](image)

**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 stage 1-3 with a corresponding HR for VT of 2.8 (95% CI 2.0-7.3) for CKD stage 1-3 compared
to 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 stage 1, 2, and 3. Figure 3 shows adjusted HRs with 95% CIs for CKD stages 1, 2, and 3, the latter with or without the presence of albuminuria compared to 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.

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.

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 stage 1, 2.4 (95% CI 1.3-4.4) for stage 2, and 1.4 (95% CI 0.6-3.3) for 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 stage 1, 0.8 (95% CI 0.3-2.2) for stage 2, and 1.7 (95% CI 0.8-3.9) for stage 3.

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

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

CKD indicates chronic kidney disease and VT indicates venous thrombosis
*Adjusted for age, sex, and body mass index, hypertension, diabetes, malignancy, and hsCRP

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 to 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 age, sex, BMI, hypertension, diabetes, malignancy, hsCRP, and albuminuria.
Table 3. Association between eGFR, albuminuria, and risk for venous thrombosis

<table>
<thead>
<tr>
<th>*Adjusted hazard ratios</th>
<th>estimated glomerular filtration rate (eGFR)</th>
<th>Albuminuria ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 90 ml/min</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td></td>
<td>60-90 ml/min</td>
<td>1.3 (0.7-2.3)</td>
</tr>
<tr>
<td></td>
<td>30-60 ml/min</td>
<td>1.5 (0.7-3.3)</td>
</tr>
</tbody>
</table>

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

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 to subjects with eGFR >90 ml/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 0.7-3.3). 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. and an eGFR between 60 and 90 ml/min or an eGFR between 30 and 60 ml/min were respectively 1.4 (95% CI 0.7-2.7) and 1.4 (95% CI 0.5-3.8). HRs for VT were increased in the presence of albuminuria in all eGFR categories. The age-, sex-, and BMI-adjusted HRs were 2.7 (95% CI 1.0-7.1), 2.2 (95% CI 1.1-4.7), and 3.2 (95% CI 1.3-8.3) 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 stage 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 4. Hazard ratios for venous thrombosis by decreased glomerular filtration rates and albuminuria

<table>
<thead>
<tr>
<th></th>
<th>Crude hazard ratios</th>
<th></th>
<th>*Adjusted hazard ratios</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No albuminuria</td>
<td>†Albuminuria</td>
<td>No albuminuria</td>
<td>†Albuminuria</td>
</tr>
<tr>
<td>eGFR &gt;90 ml/min/1.73 m²</td>
<td>1.0 (reference)</td>
<td>4.8 (1.9-12.4)</td>
<td>1.0 (reference)</td>
<td>3.1 (1.1-8.9)</td>
</tr>
<tr>
<td>eGFR 60-90 ml/min/1.73 m²</td>
<td>2.2 (1.2-4.1)</td>
<td>5.2 (2.6-10.5)</td>
<td>1.5 (0.7-3.1)</td>
<td>2.7 (1.2-6.1)</td>
</tr>
<tr>
<td>eGFR 30-60 ml/min/1.73 m²</td>
<td>3.6 (1.4-9.3)</td>
<td>10.3 (4.2-24.7)</td>
<td>1.4 (0.5-4.1)</td>
<td>4.1 (1.5-11.0)</td>
</tr>
</tbody>
</table>

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

In this study including 8495 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 to 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, while 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 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 MDRD based eGFR 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 GFR between 60 and 90 ml/min and 2.1 (95% CI 1.5-3.0) for subjects with GFR between 15 and 60 ml/min (CKD stage 3-4) as compared to subjects with GFR >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, however, 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, while our cohort was enriched for the presence of albuminuria. Moreover, whereas in our study albuminuria was assessed in 24hr urine samples (gold standard) that were not frozen before assessment, albuminuria was assessed by albumin-creatinine ratio in frozen samples in their study. 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 diabetics 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 stage 1 and 2 as compared to stage 3 might be surprising, the same pattern in the association between CKD and cardiovascular disease was previously found in the PREVEND study [4]. CKD patients with stage 1 and 2 were at higher risk of cardiovascular disease as compared to CKD patients with stage 3. A plausible explanation for this might be the difference in staging of CKD stage 3 and CKD stage 1 and 2. Albuminuria is necessary to define CKD stage 1 and 2, whereas only GFR is needed to define CKD stage 3 to 5. Therefore, CKD stage 3 is a heterogeneous group with subjects with and without evident kidney damage (albuminuria). We found that CKD stage 3 patients with albuminuria were at higher risk of VT as compared to CKD patients with stage 3 without albuminuria. These findings are in line with several other studies suggesting a higher risk for CKD stage 3 subjects with albuminuria as compared to CKD stage 3 subjects without albuminuria for different adverse outcomes, such as cardiovascular disease and the development of end-stage renal disease [4;19-21]. These data taken together suggest that information on albuminuria could be added to CKD stage 3 in order to improve the value of CKD staging for risk prognosis.

Several mechanisms behind the increased risk of VT in CKD are possible. First, endothelial damage could explain the increased risk of VT. It is remarkable that the association between CKD stage 1-3 and VT was comparable to 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 due 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. Like most studies, repeated measurements for a period of at least three months were not available in our study and therefore some subjects may 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 as compared to previous studies, 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, the 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 a GFR <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-hour urine samples.

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

REFERENCES


29. Poggio ED, Wang X, Greene T, Van LF, Hall PM. Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the


