Association of Mild to Moderate Chronic Kidney Disease with Venous Thromboembolism: Pooled Analysis of Five Prospective General Population Cohorts

Running title: Mahmoodi et al.; Association of CKD with VTE

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Abstract:

**Background** - Recent findings suggest that chronic kidney disease (CKD) may be associated with increased risk of venous thromboembolism (VTE). Given the high prevalence of mild-to-moderate CKD in the general population, in depth analysis of this association is warranted.

**Methods and Results** - We pooled individual participant data from five community-based cohorts from Europe (HUNT2, PREVEND and Tromsø study) and United States (ARIC and CHS study) to assess the association of estimated glomerular filtration rate (eGFR), albuminuria and CKD with objectively verified VTE. To estimate adjusted hazard ratios (HRs) for VTE, categorical and continuous spline models were fit using Cox regression with shared-frailty or random-effect meta-analysis. A total of 1,178 VTE events occurred over 599,453 person-years follow-up. Relative to eGFR 100 mL/min/1.73m², HRs for VTE were 1.29 (95%CI, 1.04-1.59) for eGFR 75, 1.31 (1.09-1.61) for 60, 1.82 (1.27-2.60) for 45 and 1.95 (1.26-3.01) for 30 mL/min/1.73m². Compared with albumin-creatinine ratio (ACR) of 5.0 mg/g, the HRs for VTE were 1.34 (1.04-1.72) for 30 mg/g, 1.60 (1.08-2.36) for 300 mg/g and 1.92 (1.19-3.09) for 1000 mg/g. There was no interaction between clinical categories of eGFR and ACR (P=0.20). The adjusted HR for CKD defined as eGFR <60 mL/min/1.73m² or albuminuria ≥30 mg/g (vs. no CKD) was 1.54 (95%CI, 1.15-2.06). Associations were consistent in subgroups according to age, gender, and comorbidities as well as for unprovoked versus provoked VTE.

**Conclusions** - Both eGFR and ACR are independently associated with increased risk of VTE in the general population, even across the normal eGFR and ACR ranges.

**Key words:** chronic kidney disease; deep vein thrombosis; epidemiology; pulmonary embolism; thromboembolism
The overall incidence rate of venous thromboembolism (VTE) in developed countries is approximately 1.5 per 1,000 person-years, varying from <0.05 in children to nearly 10.0 per 1,000 person-years in the elderly.\textsuperscript{1-4} The 28-day case-fatality rate after a first VTE is as high as 11\%.\textsuperscript{4} As none of the known VTE risk factors are present in up to 50\% of VTE cases,\textsuperscript{3} identifying novel risk factors for VTE is the focus of intensive research.

Nephrotic syndrome and overt proteinuria are well-known risk factors for VTE.\textsuperscript{5, 6} Mild to moderate chronic kidney disease (CKD) is associated with a procoagulant profile,\textsuperscript{7-12} and might therefore also be related to VTE risk. Two recent studies suggested that CKD may be associated with increased VTE risk, with some conflicting results.\textsuperscript{13-15} Of the two key CKD defining kidney measures (i.e. glomerular filtration rate [GFR] and albuminuria), in the Atherosclerosis Risks in Communities (ARIC) study, a significant association was found only between reduced GFR and VTE incidence,\textsuperscript{14} whereas in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study an association was observed only for elevated albuminuria.\textsuperscript{13} Possible explanations for these inconsistent findings might be limited statistical power of the individual studies and differences in study population characteristics or the selection of covariates.

Given the high prevalence of CKD (10 to 16\%) in the general adult population,\textsuperscript{16-19} in-depth analysis of the association of CKD with VTE incidence is warranted. Hence, we conducted an individual-level meta-analysis of five prospective general population-based cohorts with information on GFR, albuminuria and incident VTE. This report explores the separate and combined associations of GFR and albuminuria with the risk of VTE.

Methods

Study selection criteria
To select eligible studies we utilized criteria similar to those of the CKD Prognosis Consortium;\(^{20,21}\) eligible studies had to be community-based cohort studies with both baseline eGFR and urine albumin measurements. A PubMed search was performed on March 2 2010, using the following combination of terms: (eGFR OR GFR OR "glomerular filtration rate" OR "kidney function" OR "renal function" OR "microalbuminuria" OR albuminuria OR "albumin to creatinine ratio" OR ACR OR "urinary albumin concentration" OR UAC) AND ("venous thrombosis" OR "venous thromboembolism" OR "pulmonary embolism" OR "deep vein thrombosis" OR DVT) AND (adult [MeSH]) AND (humans [MeSH]). Two investigators (BKM and RTG) performed the search independently. No language or publication period restrictions were applied. Subsequently we searched general population studies, with albumin-to-creatinine ratio (ACR) ascertainment that participated in the CKD Prognosis Consortium,\(^{21}\) in PubMed for availability of VTE outcomes. Finally, additional eligible cohorts were sought during scientific meetings and via personal contacts. The ethical review committee of the University Medical Center of Groningen approved the project to receive and analyze the data. Review committees of each participating cohort approved sharing of the de-identified individual-level data and the conducted analyses presented in this paper.

**Baseline study variables**

Glomerular filtration rate (GFR) was estimated using the CKD Epidemiology Collaboration (CKD-EPI) equation that takes into account serum creatinine, age, sex and race.\(^{22}\) In 3 studies serum creatinine was not standardized to isotope dilution mass spectrometry (IDMS), hence we reduced the creatinine levels by 5%, the calibration factor used to adjust non-standardized Modification of Diet in Renal Disease (MDRD) Study samples to IDMS.\(^{23}\) In a sensitivity analysis, GFR was estimated using the MDRD equation.\(^{24}\) Albuminuria was quantified by the
ratio of urinary albumin to urinary creatinine excretion in a spot or 24 hour urine sample.\textsuperscript{25, 26} CKD was defined as eGFR <60 mL/min/1.73m\textsuperscript{2} and/or ACR ≥30 mg/g, according to prevailing guidelines.\textsuperscript{25} History of cardiovascular disease was defined as history of self-reported myocardial infarction (MI) or stroke at study baseline. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication. Diabetes mellitus was defined as fasting glucose concentration ≥7.0 mmol/L (≥126 mg/dL), non-fasting glucose concentration ≥11.1 mmol/L (≥200 mg/dL), or use of glucose lowering drugs or self-reported diabetes. Smoking was dichotomized to current smokers versus former or nonsmokers. Hypercholesterolemia was defined as total cholesterol concentration 5.0 mmol/L (193 mg/dL) or more in patients with a history of MI or stroke and as 6.0 mmol/L (232 mg/dL) or more in patients without history of MI and stroke. Body mass index (BMI) was calculated as measured body weight in kilograms divided by height in meters squared.

**Venous thromboembolism**

Only objectively verified symptomatic VTE were considered in all cohorts. Deep vein thrombosis was confirmed by compression ultrasound or venography, and pulmonary embolism by ventilation/perfusion lung scanning, angiography, spiral computed tomography or at autopsy. Major trauma, surgery, significant immobilization or active cancer in the proceeding 3 months were the main determinants for classifying VTE as provoked.\textsuperscript{4,13,27,28} Three of the 5 cohorts included additional risk factors in the definitions of provoked VTE, such as the use of oral contraceptives or hormone therapy, pregnancy, long-distance travel, active infectious disease, acute myocardial infarction, paresis/paralysis of the leg, and heart failure.\textsuperscript{13,27,28} In the absence of the aforementioned risk factors, VTE was classified as unprovoked.

**Statistical analysis**
Individual participant data from the cohorts were pooled. Cox proportional hazards models with shared frailty (i.e., random effects) were used to estimate adjusted hazard ratios (HRs) of VTE associated with eGFR, albuminuria and their combination. Individual cohort was considered as the shared frailty variable to account for between-study differences. As sensitivity analysis, continuous eGFR and ACR associations with VTE were also modeled using stratified (i.e., fixed effects) Cox proportional hazards regression.

Based on previous literature on risk factors for VTE and correlates of eGFR and ACR; age, sex, BMI, history of cardiovascular disease, hypertension, diabetes, total cholesterol, and current smoking were included in models as potential confounders.\textsuperscript{13, 14, 29} Since only 2 of the 5 studies also enrolled black participants, ethnicity specific results were presented for those 2 studies rather than including race as a covariate in the main model. In addition all eGFR models were adjusted for log-ACR, and all ACR models were adjusted for eGFR splines. To assess the shape of the relationship of eGFR and ACR with risk of VTE, we modeled eGFR and ACR using linear splines with knots at 45, 60, 75, 90 and 105 mL/min/1.73m\(^2\) for eGFR, and 10, 30, 300 and 1000 mg/g (to convert to mg/mmol multiply by 0.113) for ACR, respectively. eGFR of 100 mL/min/1.73 m\(^2\) and ACR of 5 mg/g were selected as reference points. HRs of eGFR association with VTE were estimated per 1 mL/min/1.73m\(^2\) increment of eGFR from 15 to 120 mL/min/1.73m\(^2\). HRs for the association of ACR with VTE were estimated per 8% increments of ACR from 2.5 to 1000 mg/g. Adjustment for prevalent baseline traditional VTE risk factors (ie, major trauma, surgery, significant immobilization or active cancer) was not performed because these were not uniformly available; however, given the temporary nature of these risk factors baseline prevalence of these risk factors is unlikely to influence long-term VTE risk. To quantify short-term influence of these risk factors on the association of eGFR and albuminuria with VTE,
we performed stratified analysis for provoked versus unprovoked VTE, where the definition of provoked VTE incorporated presence of the traditional VTE risk factors.

Joint effects of eGFR and ACR on VTE were investigated using cross-tabulation of eGFR and ACR categories. The interaction between eGFR and ACR was assessed by likelihood ratio tests between the models with eGFR and measured ACR with and without their product terms. This methodology was also used to assess interactions of CKD with sex, race, age, hypertension, diabetes, smoking, hypercholesterolemia, history of cardiovascular disease and BMI. Moreover, for dichotomous CKD VTE risk association, pooled estimates of the HRs and 95% CIs of individual studies were obtained from random-effect meta-analysis. Heterogeneity among studies was estimated by $\chi^2$ test and the $I^2$ statistics.\textsuperscript{30} Potential sources of heterogeneity were explored by meta-regression analysis.

Since ACR was measured in only a subset of the HUNT2 cohort, we adjusted the eGFR-VTE associations for log-ACR values based on multiple imputation.\textsuperscript{31} We created 20 complete data sets using the linear regression with the bootstrap method of the Stata “ice” command to achieve maximum accuracy for the imputed log-ACR.\textsuperscript{31,32} Subsequently the “micombine” command with Cox regression was used to obtain HRs and correct 95% CIs. Age, sex, hypertension, diabetes and history of cardiovascular disease, as well as VTE and log-transformed follow-up time were used to impute log-ACR values. To avoid potential bias due to multiple imputation, analyses of the ACR-VTE risk association was based on measured ACR values only. Statistical significance was considered as a 2-tailed $P <0.05$. All statistical analyses were performed using Stata software version 11.2 (StataCorp LP, College Station, Texas).

**Results**

**Figure 1** shows the flow diagram of the identified studies. Investigators of one of the eligible
studies could not provide data. Characteristics of the included studies are presented in Table 1. Overall, 95,154 participants (46.7% males, 96.6% Caucasians) were included with 599,453 person-years of follow-up. During follow-up, 1,178 VTE occurred, 45% were classified as unprovoked and 39% were pulmonary embolism alone or in combination with deep vein thrombosis. In all cohorts combined, 94,882 (99.7%) participants had measured eGFR data and 39,524 (41.5%) had ACR data (in HUNT2 only 15% of participants had ACR measured; n=9,737). All other variables presented in Table 1 had less than 0.8% missing values in the pooled dataset except current smoking (4.4% missing).

Estimates of adjusted HRs for VTE according to eGFR and ACR levels are presented in Figure 2. Risk of VTE started to be significantly increased at eGFR 88 mL/min/1.73m². Relative to eGFR 100 mL/min/1.73m², HRs for VTE were 1.29 (95%CI, 1.04-1.59) for eGFR 75, 1.31 (1.00-1.71) for 60, 1.82 (1.27-2.60) for 45 and 1.95 (1.26-3.01) for 30 mL/min/1.73m². Similar findings were observed in analyses using the MDRD equation-based eGFR (Supplementary Appendix, Figure 1). The interpretation of results did not change in models comparing ACR as a covariate with and without use of imputed ACR from the HUNT2 study, indicating the validity of the multiple imputation (Supplementary Appendix, Figure 2). The association of ACR splines and VTE risk was largely linear on the log-log scale, with significantly increased risk observed at ACR 14 mg/g and higher. Compared with ACR of 5.0 mg/g, the HRs for VTE were 1.34 (1.04-1.72) for 30 mg/g, 1.60 (1.08-2.36) for 300 mg/g and 1.92 (1.19-3.09) for 1000 mg/g. (Figure 2B). Results of fixed-effect Cox proportional hazards models were identical to the random-effect models (Supplemental Figure 3).

Table 2 shows the adjusted HR of VTE in clinical categories of eGFR and ACR based on K/DOQI staging. The corresponding number of VTE and total number of participants
according to these categories are presented in **Supplemental Table 1**. In general, the association of ACR with VTE risk was evident across most eGFR categories. The association between reduced eGFR and VTE risk was more obvious in those with normoalbuminuria (i.e., ACR<30mg/g). The risk increase was not clearly multiplicative with lower eGFR and higher ACR categories; tests for interaction of the separate categories \((P>0.14)\) and overall \((P=0.20)\) were not significant. The interaction of continuous eGFR with spline-terms and linear logACR was not significant \((P=0.10)\).

When we compared individuals with CKD versus no-CKD, the pooled HR for overall VTE associated with CKD was 1.54 (95%CI, 1.15-2.06) (**Figure 3**). In **Figure 4**, the impact of CKD on VTE incidence was consistent across the subgroups tested, except for a trend for BMI categories showing weaker association of CKD with VTE in subjects with BMI \(\geq 25\) versus <25 kg/m\(^2\) \((P\text{ for interaction }=0.07)\). Similarly, the significant heterogeneity observed for overall VTE among studies appeared to be due to differences in BMI across studies \((\beta=-0.23, P=0.054)\) (**Supplementary Appendix, Figure 4**).

The HRs of VTE with CKD compared to no CKD were similar for unprovoked and provoked VTE (**Figure 3**). Analyses for continuous eGFR and ACR are presented in the **supplemental Figure 5**. Similarly, the HRs of pulmonary embolism and deep vein thrombosis with CKD were similar (**Supplementary Appendix, Figure 6**). Finally, of the covariates, only BMI and age showed significant strong association with VTE in all models of eGFR and ACR (data not shown).

**Discussion**
In this individual participant meta-analysis including 95,154 participants from prospective observational studies followed for an average of 6.3 years, both eGFR and elevated albuminuria
were associated with increased risk of VTE independently of each other and traditional cardiovascular risk factors including BMI. For both eGFR and ACR, there was a dose-response relationship with increased risk of VTE starting in the non-CKD range of eGFR (i.e. ≥60 mL/min/1.73m²) and the normal range of ACR (i.e. <30 mg/g). There was no significant interaction between eGFR and ACR. CKD, defined by eGFR <60 mL/min/1.73m² and/or ACR ≥30 mg/g, was similarly associated with both provoked and unprovoked VTE and with both pulmonary embolism and deep-vein thrombosis.

In this comprehensive analysis of large prospective general population-based cohorts, a clear association of eGFR and albuminuria with risk of VTE clarifies the previous inconsistent published findings of the ARIC and PREVEND studies. In addition to ARIC and PREVEND cohorts this analysis included previously unpublished data from three additional cohorts. The association of CKD with VTE was largely consistent in presence versus absence of various traditional cardiovascular risk factors, except a trend for relatively stronger association of CKD with VTE in subjects with BMI <25 kg/m² as compared to BMI ≥25 kg/m² (P=0.07). Difference in mean BMI among studies also explained most of the variability of the CKD-VTE risk association across studies. This finding is in line with several observational studies that reported an antagonistic interaction between BMI and CKD on mortality.34

The observation that risks do not fully multiply when both eGFR is low and ACR is high might be secondary to competing risk for mortality in low eGFR and high ACR categories as well as to limited power in the low eGFR and high albuminuria categories (supplemental Table 1). However, a significant interaction between eGFR and ACR categories in relation to mortality was not observed in a recent meta-analysis.21

CKD is associated with a broad range of diseases requiring hospitalization. This may
have resulted in the association between CKD and provoked VTE. However, the association of eGFR and albuminuria with unprovoked VTE gives credence to a direct association of CKD with VTE. The high risk of VTE in individuals diagnosed with nephrotic-range proteinuria is assumed to be secondary to loss of anticoagulant proteins. The increased risk of VTE with mild to moderate CKD may be secondary to endothelial injury and/or the related changes in procoagulant proteins such increased levels of fibrinogen, factor VII, factor VIII, von Willebrand factor, and plasminogen activator inhibitor-1 or increased levels of D-dimers. An increased procoagulant state in CKD patients was also confirmed by functional coagulation assays such as prothrombin fragment 1+2, thrombin-antithrombin complex, plasmin-antiplasmin complex as well as in vitro thrombin generation assessed by calibrated automated thrombogram. The well-known link of CKD with arterial cardiovascular disease and mortality is also assumed to be at least partially due to a hypercoagulable state.

The high prevalence of CKD in the general population (10-16%) suggests that on the population level, CKD may explain a much larger proportion of VTE risk than most of the established rare hereditary VTE risk factors, such as antithrombin, protein C and protein S deficiencies. Assuming a CKD prevalence of 10% in the general population, the observed HR of 1.54 in our study corresponds to a population attributable risk of 5.1%, if the relationship is causal. In contrast to most established VTE risk factors, CKD, in particular albuminuria, is modifiable with medications (e.g., renin-angiotensin system inhibitors). In fact, losartan use in patients with overt proteinuria >2.0 g/d ameliorates the hypercoagulable state in proteinuric patients. Taken together with our findings, studies evaluating the effect of albuminuria lowering drugs on the risk of VTE in patients with mild to moderate CKD are warranted. Further, because CKD is common, based on the current findings it would be useful to assess
whether CKD might be associated with the risk of recurrent VTE.

We acknowledge that this study has limitations. First, measurement of creatinine, albuminuria and potential confounders were not standardized among all studies. For instance, some studies measured albumin and creatinine in fresh urine samples whereas other studies used frozen samples, and there was no centralized laboratory for all studies together. Care was taken, however, to use the same definitions for exposure variables and covariates across studies. Second, whereas we accounted for cardiovascular risk factors as potential confounders that are strongly associated with CKD and possibly associated with VTE, residual confounding may still remain. Although we were not able to account for hereditary thrombophilic defects, these are not known to be associated with mild to moderate CKD. In fact, one recent study reported a renoprotective effect of factor V Leiden.38 Third, event ascertainment across studies was comparable, but the definitions of unprovoked and provoked VTE were slightly different. However, we observed largely consistent findings for the association of CKD with overall, unprovoked and provoked VTE. Fourth, we are unable to account for anticoagulant medication use. However, given that CKD is associated with cardiovascular disease, ignoring anticoagulant medication use would have resulted in underestimated CKD-VTE risk association. Lastly, meta-regression analysis that explored the variation of HRs across studies was underpowered given the small number of studies in current analysis. Nevertheless, the association of BMI with the variation of HRs of the association of CKD with VTE risk reached borderline significance, suggesting that the heterogeneity across studies might be secondary to differences in mean BMI.

In conclusion, both eGFR and ACR are independently associated with increased risk of VTE in the general population, even in the non-CKD rage of eGFR and the normal range of ACR.
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Tromsø Study: The Tromsø Study is funded by the University of Tromsø and supported by grants from the Northern Norwegian Regional Health Authority.

Conflict of Interest Disclosures: None

References:


Table 1. Study characteristics per cohort.

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<th>Country of origin</th>
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<th>CHS*</th>
<th>HUNT2</th>
<th>PREVEND</th>
<th>Tromsø</th>
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<td>USA</td>
<td>Norway</td>
<td>Netherlands</td>
<td>Norway</td>
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**Baseline characteristics**

- Participants, n: 11,513, 3,450, 64,793, 8,573, 6,825
- Male, %: 44.1, 39.7, 46.9, 49.0, 49.2
- Mean age, years: 62.8, 78.1, 50.2, 49.0, 60.2
- Black, %: 22.5, 16.6, 0.0, 1.0, 0.0
- Hypertension, %: 47.7, 72.5, 45.1, 34.1, 50.2
- Diabetes, %: 16.8, 22.2, 3.0, 4.4, 3.4
- Hypercholesterolemia, %: 21.2, 27.3, 46.6, 37.9, 70.8
- Current smoking, %: 14.8, 7.6, 29.8, 34.2, 31.8
- History of MI or stroke, %: 10.1, 16.5, 4.9, 4.5, 8.5
- Mean body mass index, kg/m²: 28.8, 26.9, 26.3†, 26.1, 26.0
- Mean total cholesterol, mg/dL: 200, 203, 228, 218, 259
- Mean eGFR, mL/min/1.73m²: 84.3, 67.6, 97.9, 88.8, 92.8
- Median ACR, mg/g: 3.7, 10.2, 7.7, 7.0, 5.4

**Mean follow-up, years**

- 8.0, 4.5, 5.2, 9.3, 10.8

**Venous thromboembolism, n**

- 260, 61, 509, 122, 226

MI denotes myocardial infarction and ACR, albumin:creatinine ratio. eGFR was estimated by the CKD-EPI equation. To convert total cholesterol to mmol/L multiply by 0.0259. To convert ACR to mg/mmol multiply by 0.113.

* Since albuminuria was measured at visit 4 in ARIC and the year 7 CHS, we treated these visits as the baseline for ARIC and CHS.

† In subject with measured ACR in HUNT2 study, mean BMI was 28 kg/m² as depicted in supplementary Figure 4.

Table 2. Pooled estimates of adjusted hazard ratios (95% CIs) for venous thromboembolism according to clinical categories of eGFR and ACR.

<table>
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<th>ACR</th>
<th>&lt;30 mg/g  (3.3 mg/mmol)</th>
<th>30-300 mg/g (3.4-33.8 mg/mmol)</th>
<th>&gt;300 mg/g (≥33.9 mg/mmol)</th>
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<td>eGFR</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥90 mL/min/1.73m²</td>
<td>Reference</td>
<td>1.66 (1.11-2.48)</td>
<td>1.51 (0.48-4.73)</td>
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<td>60-89 mL/min/1.73m²</td>
<td>1.15 (0.96-1.38)</td>
<td>1.47 (1.07-2.03)</td>
<td>4.38 (2.64-7.26)</td>
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<td>45-59 mL/min/1.73m²</td>
<td>1.23 (0.87-1.74)</td>
<td>1.37 (0.76-2.49)</td>
<td>1.51 (0.48-4.77)</td>
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<tr>
<td>30-44 mL/min/1.73m²</td>
<td>2.13 (1.26-3.62)</td>
<td>2.11 (0.95-4.95)</td>
<td>2.33 (0.74-7.34)</td>
</tr>
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</table>

eGFR denotes estimated glomerular filtration rate and ACR, albumin:creatinine ratio. From the HUNT2 study only subjects with measured ACR contributed to this analysis. eGFR was estimated by the CKD-EPI equation. Given the low numbers of individual with eGFR<30 (see supplemental Table 1), these individuals were excluded from this analysis.
Figure Legends:

Figure 1. Flow diagram for selection of studies. * Reference 14 included analysis of 2 cohorts.

Figure 2. Pooled hazard ratios and 95% CIs for venous thromboembolism according to spline estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR). Hazard ratios and 95% CIs (error bars) according to eGFR (A) and ACR (B) adjusted for each other, age, sex, body mass index, history of cardiovascular disease, hypertension, diabetes, smoking, and total cholesterol. The reference (diamond) was eGFR 100 mL/min/1.73 m² and ACR 5 mg/g (0.6 mg/mmol), respectively. Red dots represent statistically significance. Num Part and Num VTE denote the number of participants and number of VTE, respectively, in the range between the knots represented by the vertical gray lines. To convert ACR to mg/mmol multiply by 0.113.

Figure 3. Overall and study-specific hazard ratios for overall, unprovoked and provoked venous thromboembolism in participants with CKD compared to those without CKD. CKD was defined by eGFR of <60 mL/min/1.73m² and/or ACR ≥30 mg/g. Hazard ratios are adjusted for age, sex, body mass index, history of cardiovascular disease, hypertension, diabetes, smoking, and total cholesterol. The slight differences in numbers with Table 1 are due to missing observations for either eGFR or ACR, and because for defining non-CKD both eGFR and ACR were required. For HUNT2 study only measured ACR was considered in this analysis.

Figure 4. Association of CKD with VTE in subgroups according to traditional cardiovascular risk factors. CVD denotes cardiovascular disease. CKD was defined by eGFR of <60 mL/min/1.73m² and/or ACR ≥30 mg/g. Hazard ratios are adjusted for other than the stratified risk factor itself, which included age, sex, body mass index, history of cardiovascular disease, hypertension, diabetes, smoking, and total cholesterol. *Race comparison was limited to ARIC and CHS studies, since the other studies enrolled only whites.
199 Citations identified through PubMed search

- 197 excluded after title and abstract screen (did not fulfill inclusion criteria)

- 3 general population cohorts identified with information on eGFR, albuminuria and VTE\(^{13,14}\)\

  - 1 additional cohort\(^{28}\) identified from screening of 14 general population cohorts from CKD Prognosis Consortium\(^{21}\)

  - 2 additional cohorts\(^{27,33}\) identified via personal contacts and scientific meetings

  - 1 cohort unable to provide data\(^{33}\)

5 cohorts included in the analysis
<table>
<thead>
<tr>
<th>Study</th>
<th>VTE</th>
<th>CKD</th>
<th>Participants</th>
<th>Hazard ratio (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
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<tr>
<td><strong>Overall VTE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIC</td>
<td>260</td>
<td>1516</td>
<td>11414</td>
<td>1.10 (0.78, 1.55)</td>
<td>22.05</td>
</tr>
<tr>
<td>CHS</td>
<td>59</td>
<td>1392</td>
<td>3156</td>
<td>1.95 (1.12, 3.40)</td>
<td>14.74</td>
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<tr>
<td>HUNT2</td>
<td>181</td>
<td>3487</td>
<td>11246</td>
<td>1.16 (0.84, 1.61)</td>
<td>22.84</td>
</tr>
<tr>
<td>PREVEND</td>
<td>121</td>
<td>1133</td>
<td>8540</td>
<td>2.32 (1.54, 3.50)</td>
<td>19.52</td>
</tr>
<tr>
<td>Tromso</td>
<td>225</td>
<td>593</td>
<td>6797</td>
<td>1.73 (1.19, 2.52)</td>
<td>20.84</td>
</tr>
<tr>
<td>Subtotal (I-squared = 64.3%, p = 0.024)</td>
<td></td>
<td></td>
<td></td>
<td>1.54 (1.15, 2.06)</td>
<td>100.00</td>
</tr>
<tr>
<td><strong>Unprovoked VTE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIC</td>
<td>92</td>
<td>1488</td>
<td>11246</td>
<td>1.09 (0.60, 1.96)</td>
<td>20.59</td>
</tr>
<tr>
<td>CHS</td>
<td>20</td>
<td>1370</td>
<td>3116</td>
<td>2.42 (0.92, 6.32)</td>
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<tr>
<td>HUNT2</td>
<td>104</td>
<td>3447</td>
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<td>1.04 (0.68, 1.60)</td>
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<tr>
<td>PREVEND</td>
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<td>1115</td>
<td>8479</td>
<td>2.41 (1.37, 4.24)</td>
<td>21.52</td>
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<tr>
<td>Tromso</td>
<td>90</td>
<td>570</td>
<td>6662</td>
<td>1.52 (0.81, 2.84)</td>
<td>19.26</td>
</tr>
<tr>
<td>Subtotal (I-squared = 45.8%, p = 0.117)</td>
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<td></td>
<td></td>
<td>1.48 (1.03, 2.13)</td>
<td>100.00</td>
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<tr>
<td><strong>Provoked VTE</strong></td>
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<td></td>
<td></td>
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<tr>
<td>ARIC</td>
<td>168</td>
<td>1502</td>
<td>11322</td>
<td>1.11 (0.72, 1.69)</td>
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<tr>
<td>CHS</td>
<td>39</td>
<td>1379</td>
<td>3135</td>
<td>1.75 (0.88, 3.48)</td>
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<tr>
<td>HUNT2</td>
<td>77</td>
<td>3444</td>
<td>11142</td>
<td>1.36 (0.82, 2.24)</td>
<td>21.03</td>
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<tr>
<td>PREVEND</td>
<td>61</td>
<td>1109</td>
<td>8480</td>
<td>2.21 (1.21, 4.03)</td>
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<tr>
<td>Tromso</td>
<td>135</td>
<td>581</td>
<td>6707</td>
<td>1.88 (1.17, 3.00)</td>
<td>23.43</td>
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<tr>
<td>Subtotal (I-squared = 16.9%, p = 0.307)</td>
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<td></td>
<td></td>
<td>1.54 (1.19, 1.99)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Strata</th>
<th>Number of VTE</th>
<th>Number of Participants</th>
<th>Adjusted HR (95% CI)</th>
<th>P-value for interaction</th>
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<tr>
<td>Sex</td>
<td>Female</td>
<td>457</td>
<td>22219</td>
<td>1.44 (1.14, 1.82)</td>
<td>0.52</td>
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<tr>
<td></td>
<td>Male</td>
<td>389</td>
<td>18934</td>
<td>1.48 (1.16, 1.89)</td>
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<td>Race*</td>
<td>White</td>
<td>223</td>
<td>11481</td>
<td>1.24 (0.87, 1.76)</td>
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<td></td>
<td>Black</td>
<td>96</td>
<td>3089</td>
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<td>Age</td>
<td>&lt;65</td>
<td>352</td>
<td>23375</td>
<td>1.82 (1.35, 2.45)</td>
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<tr>
<td></td>
<td>≥65</td>
<td>494</td>
<td>17778</td>
<td>1.55 (1.28, 1.89)</td>
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<tr>
<td>BMI</td>
<td>&lt;25</td>
<td>166</td>
<td>13340</td>
<td>1.68 (1.12, 2.50)</td>
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<td></td>
<td>≥25</td>
<td>680</td>
<td>27813</td>
<td>1.46 (1.21, 1.75)</td>
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<td>Hypertension</td>
<td>No</td>
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<td>17858</td>
<td>1.74 (1.24, 2.45)</td>
<td>0.12</td>
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<tr>
<td></td>
<td>Yes</td>
<td>546</td>
<td>23190</td>
<td>1.39 (1.15, 1.69)</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>No</td>
<td>429</td>
<td>22694</td>
<td>1.39 (1.09, 1.77)</td>
<td>0.97</td>
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<tr>
<td></td>
<td>Yes</td>
<td>417</td>
<td>18459</td>
<td>1.54 (1.22, 1.95)</td>
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<tr>
<td>Diabetes</td>
<td>No</td>
<td>729</td>
<td>35844</td>
<td>1.44 (1.19, 1.73)</td>
<td>0.81</td>
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<td></td>
<td>Yes</td>
<td>111</td>
<td>4941</td>
<td>1.56 (1.04, 2.32)</td>
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<td>Smoking</td>
<td>No</td>
<td>692</td>
<td>31120</td>
<td>1.42 (1.18, 1.71)</td>
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<td></td>
<td>Yes</td>
<td>143</td>
<td>9130</td>
<td>1.92 (1.28, 2.86)</td>
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<tr>
<td>History of CVD</td>
<td>No</td>
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<td>36520</td>
<td>1.43 (1.18, 1.72)</td>
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<tr>
<td></td>
<td>Yes</td>
<td>112</td>
<td>4308</td>
<td>1.62 (1.07, 2.45)</td>
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</tr>
</tbody>
</table>
Association of Mild to Moderate Chronic Kidney Disease with Venous Thromboembolism: Pooled Analysis of Five Prospective General Population Cohorts

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SUPPLEMENTAL MATERIAL

Supplement to: Association of Mild to Moderate Chronic Kidney Disease with Venous Thromboembolism: Pooled Analysis of Five Prospective General Population Cohorts.
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Supplemental Table 1. Number of VTE and total number of participants according to clinical categories of eGFR and ACR.

<table>
<thead>
<tr>
<th>ACR</th>
<th>N VTE/ Participants</th>
<th>N VTE/ Participants</th>
<th>N VTE/ Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 mg/g (&lt;3.3 mg/mmol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-300 mg/g (3.4-33.8 mg/mmol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;300 mg/g (≥33.9 mg/mmol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥90 mL/min/1.73m²</td>
<td>235/16,058</td>
<td>27/1,060</td>
<td>3/110</td>
</tr>
<tr>
<td>60-89 mL/min/1.73m²</td>
<td>368/16,764</td>
<td>52/1,824</td>
<td>17/247</td>
</tr>
<tr>
<td>45-59 mL/min/1.73m²</td>
<td>44/1,783</td>
<td>12/452</td>
<td>3/114</td>
</tr>
<tr>
<td>30-44 mL/min/1.73m²</td>
<td>16/402</td>
<td>6/165</td>
<td>3/91</td>
</tr>
<tr>
<td>&lt;30 mL/min/1.73m²</td>
<td>1/41</td>
<td>2/56</td>
<td>1/84</td>
</tr>
</tbody>
</table>

eGFR denotes estimated glomerular filtration rate, ACR, albumin to creatinine ratio; N VTE, number of venous thromboembolism and N total, total number of participants. From the HUNT2 study only the sample with measured ACR was included.
Supplemental Figure 1. Pooled hazard ratios and 95% CIs for venous thromboembolism according to spline estimated glomerular filtration rate (eGFR) by CKD-EPI equation versus MDRD equation.

Hazard ratios and 95% CIs according to CKD-EPI equation based eGFR (black line with cyan shaded area) and MDRD equation based eGFR (red line with error bars). Hazard ratios are adjusted for age, sex, body mass index, history of cardiovascular disease, hypertension, diabetes, smoking, total cholesterol and log-ACR. The reference (diamond) was eGFR 100 mL/min/1.73 m$^2$. The black and red circles denote statistical significance of the hazard ratios according to CKD-EPI and MDRD equations based eGFR, respectively.
Supplemental Figure 2. Ratio of the hazard ratios for venous thromboembolism according to spline estimated glomerular filtration rate (eGFR) in the sample with measured albumin to creatinine ratio (ACR) versus the total sample with imputed log-ACR in the HUNT2 study.

To evaluate the effect of imputed log-ACR on the eGFR-VTE risk association versus the impact of measured log-ACR, eGFR associated hazard ratios of model 1 were divided by the eGFR related hazard ratios of model 2 in the measured ACR sample (cyan line) and the total sample with imputed log-ACR (gray dashed line) in the HUNT2 study.

Model 1: eGFR splines, age, sex, body mass index, history of cardiovascular disease, hypertension, diabetes, smoking and total cholesterol.

Model 2: variables from model 1+log-ACR.
Supplemental Figure 3. Pooled hazard ratios and 95% CIs for venous thromboembolism according to spline estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR).

Results are from fixed-effect (strata) Cox proportional hazard regression. Results of random-effect (shared frailty) Cox proportional hazard regression are presented in Figure 2 in the main paper. Hazard ratios and 95% CIs (error bars) according to eGFR (A) and ACR (B) adjusted for each other, age, sex, body mass index, history of cardiovascular disease, hypertension, diabetes, smoking, and total cholesterol. The reference (diamond) was eGFR 100 mL/min/1.73 m$^2$ and ACR 5 mg/g (0.6 mg/mmol), respectively. Red dots denote statistical significance. To convert ACR to mg/mmol multiply by 0.113.
Supplemental Figure 4. Meta-regression of adjusted hazard ratios for venous thromboembolism in subjects with chronic kidney disease versus subjects without chronic kidney disease on mean body mass index (BMI).

Hazard ratios are adjusted for age, sex, body mass index, history of cardiovascular disease, hypertension, diabetes, smoking and total cholesterol.
Supplemental Figure 5. Pooled hazard ratios and 95% CIs for idiopathic versus provoked venous thromboembolism (VTE) according to spline estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR).

Hazard ratios and 95% CIs according to eGFR (A) and ACR (B) adjusted for each other, age, sex, body mass index, history of cardiovascular disease, hypertension, diabetes, smoking, and total cholesterol. Hazard ratios for provoked and idiopathic VTE are depicted by black line with cyan-shaded area and redline with error bars, respectively. The reference (diamond) was eGFR 100 mL/min/1.73 m² and ACR 5 mg/g (0.6 mg/mmol), respectively. The black and red circles denote statistical significance for provoked and unprovoked VTE, respectively. To convert ACR in mg/g to mg/mmol multiply by 0.113.
Supplemental Figure 6. Overall and study-specific hazard ratios for pulmonary embolism, and deep-vein thrombosis in CKD subjects as compared with subjects without CKD.

Hazard ratios are adjusted for age, sex, body mass index, history of cardiovascular disease, hypertension, diabetes, smoking, and total cholesterol.