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Cystatin C is associated with risk of venous thromboembolism in subjects with normal kidney function – the Tromsø Study

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Abstract

Background. Previous studies have reported an association between impaired kidney function, assessed by cystatin C based estimated glomerular filtration rate, and venous thromboembolism. The aim of our study was to investigate whether serum cystatin C was associated with risk of venous thromboembolism among subjects with normal kidney function in a prospective population-based study.

Design and Methods. Cystatin C was measured in serum from 3251 men and women with normal kidney function, aged 25-84 years, who participated in the Tromsø Study in 1994-95. Normal kidney function was defined as creatinine based estimated glomerular filtration rate > 90 ml/min/173m² and absence of microalbuminuria. Incident venous thromboembolism was registered from the date of inclusion through the end of follow-up, September 1, 2007. Cox-regression models were used to calculate hazard ratios with 95% confidence interval for venous thromboembolism.

Results. There were 83 incident venous thromboembolic-events, of which 53 (63.9 %) were provoked, during a median of 12.3 years of follow-up. One standard deviation (0.11 mg/L) increase in serum cystatin C levels were associated with a 43% (hazard ratio 1.43, 95% confidence interval 1.17-1.72) increased risk of total venous thromboembolism. Subjects with cystatin C ≥ 0.87 mg/L (upper quartile) had 2.5-fold (hazard ratio 2.51, 95% confidence interval: 1.27-4.96) increased risk of venous thromboembolism compared to those ≤ 0.72 mg/L (lower quartile) in adjusted analysis. The risk estimates were even higher for provoked venous thromboembolism (hazard ratio 3.11, 95% confidence interval 1.23-7.86).
**Conclusions.** Serum cystatin C was associated with risk of venous thromboembolism in subjects with normal kidney function. Our findings suggest that elevated serum cystatin C levels may promote venous thrombosis beyond reflecting impaired kidney function.

**Introduction**

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a common disease with serious short- and long-term complications and potential fatal outcome (1, 2). The incidence of VTE is 1 to 3 per 1000 person-years with a steep incline with age (1, 2). Even though many environmental and inherited predisposing factors have been associated with VTE (1-5), still 30–50% of the events have no obvious provoking factors (6-8).

Cystatin C (CysC) is a non-glycosylated cysteine protease inhibitor with a low molecular weight of 13 kDa synthesized at a constant rate (housekeeping gene product) by most nucleated cells (9). Although reported to be unaffected by gender, age or muscle mass (10, 11), recent studies have shown higher concentrations of CysC in men, and to be associated with increasing height, weight, and age (12-14). Impaired renal function, assessed by estimated GFR (eGFR) based on serum CysC concentrations, is associated with increased risk of future arterial cardiovascular disease (15). Observational studies also suggest that serum CysC predict arterial cardiovascular disease in subjects with normal kidney function (16).
Previous studies have shown diverging results on the relation between mildly impaired kidney function based on CysC and risk of VTE (17, 18). Serum CysC was not associated with risk of VTE in the Cardiovascular Health Study (CHS) (17). However, eGFR based on serum CysC was associated with 1.6-fold increased risk of total VTE in severe kidney disease in the Atherosclerosis Risk in Communities (ARIC) study (18). Although renal dysfunction appears to be the most plausible link between increased CysC and VTE, the predictive value of CysC for VTE in a population with normal kidney function has not been elucidated. The aim of our study was to investigate whether serum CysC was associated with risk of VTE among subjects with normal kidney function in a prospective population-based study.

**Design and Methods**

**Study population**

Participants were recruited from the fourth survey of the Tromsø Study (conducted in 1994-95), a single-centre prospective, population-based study, with repeated health surveys of the inhabitants of Tromsø, Norway. All inhabitants aged >24 years were invited, and 27 158 (77% of the eligible population) participated. The participants aged 55–74 years and 5–10% of the other birth cohorts (n=9057) were invited to a more extensive visit 3–12 weeks later, and 75% (n=6889) attended. Subjects who did not consent to medical research (n=23), subjects not officially registered inhabitants of the municipality of Tromsø at baseline (n=16), subjects with a previous history of VTE (n=18), subjects with missing values of CysC or serum creatinine (n=210) and subjects with GFR <90 ml/min and microalbuminuria (n=3321) were excluded from the study. Thus, 3251 subjects were included in the study, and incident VTE events among the study participants were
recorded from the date of enrolment to the end of follow up, 1st of September 2007. The study was approved by the regional committee for research ethics, and all participants gave written informed consent to participate.

Measurements

Height and weight were measured with subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms, divided by the square of height in meters (kg/m²). Information on self-reported diabetes, current daily smoking (pipe/cigar/cigarettes), current hormone therapy and prior cardiovascular disease (myocardial infarction, angina pectoris or stroke) was collected through a self-administered questionnaire. Hormone therapy was defined as self-reported current use of estrogen supplementation (tablets or patches) or current use of oral contraceptives. Blood pressure and non-fasting serum lipids were measured as previously described (19). Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or the use of antihypertensives. CysC was measured by particle-enhanced turbidimetric immunoassay using reagents from Gentian (Gentian, Moss, Norway) on a Modular E analyzer (Roche Diagnostics). Inter-assay coefficient of variation was 5.0 %. High sensitivity C-reactive protein (hs-CRP) was measured by a particle-enhanced turbidimetric immunoassay on a Modular P autoanalyzer (Roche/Hitachi), using reagents from Roche Diagnostics GmbH, Mannheim, Germany.
Assessment of renal function

Plasma creatinine was analyzed by a modified Jaffé reaction, but a subsample was reanalyzed with an enzymatic method, and recalculated creatinine values (20) were used for estimation of glomerular filtration rate (eGFRcrea). eGFRcrea was calculated from the recalibrated four-variable Modification of Diet in Renal Disease (MDRD) study equation; eGFRcrea = 175 x (s-creatinine (µmol/l)/88.4) ^{-1.154} x age^{-0.203} x (0.742 if female) (21). Chronic kidney disease (CKD) was categorized based on the National Kidney Foundation guidelines (22) using eGFRcrea; eGFR ≥90 ml/min/1.73m² for normal kidney function, eGFR between 60 and 89 ml/min/1.73m² for mildly impaired kidney function, and eGFR between 15 and 59 ml/min/1.73m² for stage 3/4 CKD.

Three samples of morning spot-urine, collected on consecutive days, were tested with a dipstick and analyzed immediately for albumin and creatinine, using commercial kits (ABX Diagnostics; Montpellier, France). One urine-sample was cultured. Albumin–creatinine ratio (ACR) was calculated for each urine-specimen, and the mean ACR value (mg/mmol) was used in the analyses. Normal kidney function was defined as creatinine based estimated glomerular filtration rate >90 ml/min/173m² and absence of microalbuminuria (albumin-creatinine ratio ≥1.92 mg/mmol in women and ≥2.83 mg/mmol in men).
Venous thromboembolism ascertainment

All first lifetime events of VTE during follow-up were identified as previously described (19) by searching the hospital discharge diagnosis registry, the autopsy registry, and the radiology procedure registry at the University Hospital of North Norway.

The medical records for each potential VTE-case were reviewed by trained personnel. For subjects derived from the hospital discharge diagnosis registry and the radiology procedure registry, an episode of VTE was verified and recorded as a validated outcome when all four of the following criteria were fulfilled: (i) objectively confirmed by diagnostic procedures (compression ultrasonography, venography, spiral-computed tomography (CT), perfusion-ventilation scan, pulmonary angiography or autopsy); (ii) the medical record indicated that a physician had made a diagnosis of DVT or PE; (iii) signs and symptoms consistent with DVT or PE were present; (iv) therapy with anticoagulants (heparin, warfarin, or similar agent) thrombolytics, or vascular surgery was required. For subjects derived from the autopsy registry, a VTE-event was recorded as an outcome when the autopsy record indicated VTE as a cause of death or as a significant condition.

Based on the presence of provoking factors at the time of diagnosis, the VTE-event was classified as unprovoked (no provoking factors) or provoked (≥1 provoking factors). Major surgery, trauma, or acute medical condition (acute MI, ischemic stroke, or major infectious disease) within 8 weeks before event, active cancer at time of event, marked immobilization (bed rest for longer than 3 days, wheelchair, or long distant travels exceeding 4 hours within the last 14 days before event) were considered provoking factors.
Statistical analyses

Statistical analysis was carried out by the SPSS version 17.0 (SPSS Inc. Chicago, IL, USA). Baseline characteristics of participants across quartiles of serum CysC were compared using a $\chi^2$ test for categorical variables and one-way ANOVA for continuous variables.

Cox-proportional hazards regression models were used to estimate hazard ratios (HR), with 95% confidence interval (CI), for unprovoked-, provoked- and total VTE by quartiles of CysC. In the Cox-models, the lowest quartile of CysC was used as reference group. Hazard ratios (HRs) for the associations between CysC and risk of VTE were primarily adjusted for age and sex, and subsequently for additional potential confounders such as BMI, hs-CRP, diabetes and hypertension. The proportional hazard assumption was verified by evaluating the parallelism between the curves of the log-log survivor function for quartiles of CysC.

Results

There were 83 incident VTE-events during a median of 12.3 years of follow-up. The overall crude incidence rate of VTE was 2.6 per 1000 person-years.

Baseline characteristics of participants across quartiles of CysC are shown in Table 1. Age, BMI, blood pressure, hs-CRP, and the proportions of males and smokers increased across quartiles of CysC (all P-values for trend <0.001)(Table 1).
Among the VTE patients, 61.4% had DVT and 38.6% had pulmonary embolism with or without concurrent DVT (table 2). A total of 30 (36.1%) events were unprovoked (Table 2). Cancer was the most common provoking factor (26.5% of the VTE patients had a cancer-related VTE event), followed by surgery (22.9%) (Table 2).

The risk of total VTE increased significantly across quartiles of CysC (p for trend across categories 0.002) in analysis adjusted for age and sex (Table 3), and were only moderately attenuated by further adjustment for BMI, smoking, diabetes and hs-CRP (p for trend 0.001). Subjects with CysC ≥0.87 mg/L (upper quartile) had a 2.5-fold increased risk of VTE compared to those ≤0.72 mg/L (lower quartile) (HR 2.51, 95% CI: 1.27-4.96) adjusted for age, sex, BMI, smoking, diabetes and hs-CRP. The risk estimates were even higher for provoked VTE (HR 3.11, 95% CI: 1.23-7.86). Moreover, when analyzing CysC as a continuous variable, 1 standard deviation (SD) (0.11 mg/L) increase in CysC was associated with a 46% increased risk of total VTE, 45% increased risk of provoked VTE, and 48% increased risk of unprovoked VTE. The risk estimates for unprovoked VTE across quartiles of CysC did not reach statistical significance (Table 3).

Cumulative incidences of VTE by quartiles of CysC are shown in Figure 1. The curves diverged progressively during the entire observation period. During a maximum of 12.3 years of follow-up, 1% of participants in the lowest quartiles (Q1 and Q2), 1.5% of those in Q3 and 5% of those in the highest quartile (Q4) developed VTE (Figure 1).


Discussion

The present study is, to the best of our knowledge, the first to identify CysC as a risk factor for VTE in subjects with normal kidney function in a prospective, population-based study. The association between serum CysC and risk of VTE held true in statistical models treating CysC both as a continuous and categorized variable, and after adjustment for potential confounders. During follow-up, there was a stepwise increase in incident events by increasing levels of CysC. The cumulative incidence was 5% in the highest quartile (CysC ≥0.87 mg/L) compared with 1% in the lowest quartile (CysC <0.72 mg/L). Our findings suggest that elevated serum CysC levels may promote venous thrombosis independent of impaired kidney function.

Increased levels of CysC are found in patients with coronary artery disease (15, 23, 24), and CysC has been identified as a risk factor for myocardial infarction, and stroke (25-27). Moreover, increased CysC was associated with all-cause, cardiovascular, and even non-cardiovascular mortality in a population-based cohort of subjects with normal kidney function (28). However, whether CysC merely reflects the association of mildly impaired kidney function with increased risk for CVD, or is an independent risk factor involved in the pathogenesis of atherosclerosis, has not been fully elucidated. CysC is an endogenous inhibitor of potential destructive proteases such as cathepsins, and is severely reduced and associated with abundant levels of cathepsins in atherosclerotic lesions (29). The positive association between serum CysC and risk of cardiovascular diseases is suggested to represent a compensatory mechanism to reduce pro-atherogenic cathepsin activity (30).
Although the mechanisms through which elevated CysC relates to venous thrombosis remains unclear, it is tempting to speculate that other pathophysiologic pathways independent of impaired GFR are involved. Beyond reflecting impaired kidney function, CysC has been associated with chronic low-grade inflammation and atherosclerosis (31). Accordingly, we found a linear increase in hs-CRP across categories of elevated CysC (table 1). Adjustment for hs-CRP in the statistical models did not affect the risk estimates for VTE by CysC, indicating that low-grade downstream inflammation, assessed by hs-CRP, is not a substantial contributor to risk mediated by CysC. CysC is also abundantly secreted by human adipose tissue explants in vitro (32), and according to our findings (table 1) positively associated with BMI. Adjustment for BMI did not affect the risk estimates for VTE by CysC, suggesting that this association was not mediated by BMI. Recently, neutrophil proteases, in concert with externalized nucleosomes, were shown to promote thrombus formation inside blood vessels (33). CysC is known to modulate neutrophil chemotactic activity (34) and may inhibit prothrombotic activity of proteolytic substances secreted by activated neutrophils. Thus, it may be hypothesized that increased serum levels of CysC represent an inadequate counterbalance mechanism to avoid thrombosis formation.

The main strengths of our study are the large number of participants and validated VTE events, the prospective design, and long term follow-up. The study was performed in a population generally without previous diagnosis of CKD. The study has, however, some limitations. First, there are potential sources of misclassification. Renal function estimated by the Modification of Diet in Renal Disease (MDRD) formula and serum creatinine is not as accurate as a direct measurement from iothalamate or creatinine clearance using a 24-h urine collection. However, direct measurement of
GFR is not feasible in a large epidemiological study. Furthermore, estimation of renal function was based on only one measure of serum creatinine, and may be subject to intraindividual variation. A possible change in kidney function during the study period could have resulted in misclassification of CKD status, and thereby underestimation of our risk estimates due to regression towards the null hypothesis.

In conclusion, our prospective population-based study showed that CysC was associated with risk of VTE among subjects with normal kidney function. Our findings suggest that elevated serum CysC levels may predict venous thrombosis beyond reflecting impaired kidney function.

**Authorship and Disclosures**

EEB wrote the manuscript, performed the statistical analyses and takes primary responsibility for the manuscript. SKB acquired data and participated in statistical analyses. AV participated in statistical analysis. JB participated in the laboratory work. JBH acquired data and coordinated the research. All authors have made critical revisions of the manuscript and approved the final version.

The authors reported no potential conflicts of interest.
References


**Table 1.** Baseline characteristics across quartiles of Cystatin C. The Tromsø Study 1994-2007. Values are means with standard deviations (SD) in brackets for continuous variables and percentages with numbers in brackets for dichotomized variables.

<table>
<thead>
<tr>
<th>Quartiles of Cystatin C (mg/L)</th>
<th>≤ 0.72</th>
<th>0.73-0.79</th>
<th>0.80-0.86</th>
<th>≥ 0.87</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, no</td>
<td>830</td>
<td>821</td>
<td>789</td>
<td>811</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cystatin C, mg/L (SD)</td>
<td>0.66(0.046)</td>
<td>0.76(0.019)</td>
<td>0.82(0.019)</td>
<td>0.94(0.075)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years (SD)</td>
<td>54(11)</td>
<td>57(11)</td>
<td>58(10)</td>
<td>61(9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex, % (n)</td>
<td>41.8(347)</td>
<td>53.7(441)</td>
<td>62.0(489)</td>
<td>66.8(542)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, % (n)</td>
<td>28(232)</td>
<td>34(279)</td>
<td>39(308)</td>
<td>42(342)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m² (SD)</td>
<td>25.3(3.7)</td>
<td>25.8(3.9)</td>
<td>26.0(4.0)</td>
<td>26.2(4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, % (n)</td>
<td>2.3(20)</td>
<td>2.2(18)</td>
<td>2.4(19)</td>
<td>2.3(23)</td>
<td>0.86</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg (SD)</td>
<td>136(20)</td>
<td>139(20)</td>
<td>139(20)</td>
<td>143(22)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg (SD)</td>
<td>79(11)</td>
<td>80(12)</td>
<td>80(12)</td>
<td>82(13)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hs-CRP, mg/L (SD)</td>
<td>1.88(64.8)</td>
<td>1.94(4.14)</td>
<td>2.30(5.0)</td>
<td>3.41(6.61)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Table 2. Characteristics of VTE patients (n= 83), at the time of the VTE-event. The Tromsø Study, 1994-2007. Values are percentages with numbers in brackets.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>44 (1432)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>61.4 (51)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>38.6 (32)</td>
</tr>
<tr>
<td>Unprovoked VTE</td>
<td>36.1 (30)</td>
</tr>
</tbody>
</table>

Clinical risk factors:

- Estrogens*                             | 12.9 (4) |
- Heredity†                              | 3.6 (3) |
- Pregnancy                              | 0 |
- Other medical condition‡               | 25.3 (21) |

Provoking factors:

- Surgery                                | 22.9 (19) |
- Trauma                                 | 3.6 (3) |
- Acute medical condition                | 21.7 (18) |
- Cancer                                 | 26.5 (22) |
- Immobilization (bed rest>3 days, wheelchair) | 9.6 (8) |
- Other§                                 | 3.6 (3) |

*Hormone replacement therapy/oral contraceptives.
†Heredity: Family history of VTE in first degree relative before the age of 60 years.
‡Other diseases within the previous year (myocardial infarction, ischemic stroke, heart failure, inflammatory bowel disease, chronic infections, chronic obstructive pulmonary disease or myeloproliferative disorders).
§Other factor specifically described as provoking in the medical record (e.g intravascular catheter)
Table 3. Age and sex adjusted incidence rates (IR) and hazard ratios (HR) with 95 % confidence interval (CI) for VTE by quartiles of Cystatin C. The Tromsø Study 1994-2007.

<table>
<thead>
<tr>
<th>Quartile range Cystatin C (mg/L)</th>
<th>Subjects</th>
<th>VTE events</th>
<th>IR (95 % CI)*</th>
<th>HR (95 % CI)*</th>
<th>HR (95 % CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 0.72</td>
<td>830</td>
<td>12</td>
<td>1.26 (0.69-2.32)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>0.73-0.79</td>
<td>821</td>
<td>14</td>
<td>1.28 (0.71-2.32)</td>
<td>1.01 (0.46-2.20)</td>
<td>1.02 (0.47-2.22)</td>
</tr>
<tr>
<td>0.80-0.86</td>
<td>789</td>
<td>18</td>
<td>1.60 (0.91-2.81)</td>
<td>1.26 (0.60-2.05)</td>
<td>1.30 (0.61-2.71)</td>
</tr>
<tr>
<td>≥ 0.87</td>
<td>811</td>
<td>39</td>
<td>3.11 (1.91-5.04)</td>
<td>2.46 (1.26-4.83)</td>
<td>2.51 (1.27-4.96)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
<td>0.001</td>
</tr>
<tr>
<td>Per 1SD increase in CysC</td>
<td>83</td>
<td></td>
<td>1.45 (1.20-1.76)</td>
<td>1.46 (1.20-1.77)</td>
<td></td>
</tr>
</tbody>
</table>

| Provoked VTE                     |          |            |               |               |               |
| ≤ 0.72                           | 824      | 6          | 0.59 (0.25-1.39) | 1.00 (reference) | 1.00 (reference) |
| 0.73-0.79                        | 816      | 9          | 0.76 (0.36-1.62) | 1.28 (0.52-3.50) | 1.27 (0.45-3.60) |
| 0.80-0.86                        | 783      | 12         | 0.97 (0.47-1.98) | 1.62 (0.60-4.39) | 1.63 (0.60-4.41) |
| ≥ 0.87                           | 789      | 26         | 1.88 (1.01-3.49) | 3.15 (1.26-7.89) | 3.11 (1.23-7.86) |
| P for trend                       |          |            |                | 0.003          | 0.004          |
| Per 1SD increase in CysC         | 53       |            | 1.39 (1.11-1.74) | 1.45 (1.14-1.84) |

| Unprovoked VTE                   |          |            |               |               |               |
| ≤ 0.72                           | 824      | 6          | 0.69 (0.29-1.64) | 1.00 (reference) | 1.00 (reference) |
| 0.73-0.79                        | 812      | 5          | 0.52 (0.19-1.37) | 0.7 (0.22-2.48) | 0.77 (0.23-2.54) |
| 0.80-0.86                        | 777      | 6          | 0.62 (0.24-1.58) | 0.89 (0.28-2.81) | 0.94 (0.29-3.01) |
| ≥ 0.87                           | 785      | 13         | 1.24 (0.57-2.72) | 1.80 (0.65-4.95) | 1.95 (0.69-5.46) |
| P for trend                       |          |            |                | 0.12           | 0.14           |
| Per 1SD increase in CysC         | 30       |            | 1.43 (1.04-1.97) | 1.48 (1.08-2.05) |

1SD=0.11 mg/L
* Age and sex-adjusted
** Multivariable model adjusted for age, sex, body mass index, smoking, diabetes (BMI) and high sensitive (hs)-CRP
Figure 1. Cumulative incidence of venous thromboembolism by quartiles of cystatin C plotted against time. Data were adjusted for sex, age, smoking, BMI, diabetes and hs-CRP.