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Cystatin C and creatinine as markers of bleeding complications, cardiovascular events and mortality during oral anticoagulant treatment

Marcus Lind [a,*], Jan-Håkan Jansson [a], Torbjörn K. Nilsson [b], Lisbeth Slunga Järvholm [a], Lars Johansson [a]

[a] Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
[b] Department of Clinical Chemistry, Örebro University Hospital, Örebro, Sweden

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ABSTRACT

Introduction: Impaired kidney function has been linked to both ischemic events as well as bleeding complications in several clinical conditions. Our aim was to investigate if cystatin C, creatinine and calculated glomerular filtration rate (eGFR) were related to future risk of bleeding complications, cardiovascular events or all-cause mortality during oral anticoagulant treatment.
Materials and methods: In a cohort study, 719 patients on long-term vitamin K antagonist (VKA) treatment were followed for a mean of 4.2 years. Blood sampling was taken at inclusion and patients were followed prospectively. Cystatin C and creatinine were analysed and eGFR was calculated. All medical records were reviewed. Major bleeding events, myocardial infarctions, strokes, arterial emboli, and deaths were recorded and classified.
Results: After adjustment for age, no association between cystatin C, creatinine or eGFR and major bleeding was found. Cystatin C was independently associated with cardiovascular events (hazard ratio 1.50 (95% CI: 1.27-1.77)) and all-cause mortality (hazard ratio 1.62 (95% CI: 1.38-1.90)).Creatinine was only associated with all-cause mortality, while eGFR was not associated with any of the outcomes.
Conclusions: Our findings underscore the superiority of cystatin C as a marker of cardiovascular risk compared to creatinine or eGFR. VKA-treated patients with increased cystatin C levels should be considered to be at an increased risk of cardiovascular events, and not bleeding complications.

Introduction

Thromboembolic diseases are associated with significant mortality and morbidity [1–3]. There are several conditions in which the risk of thromboembolic events can be significantly reduced with oral anticoagulant (OAC) treatment [4]. However, the use of anticoagulation is complicated by an increased risk of serious bleeding both for vitamin K antagonists (VKA), as well as for the newer inhibitors of thrombin and factor Xa [5,6]. In order to optimize the treatment of individual patients, risk scores addressing the likelihood of thromboembolic events [7] and also the risk of bleeding complications are being implemented [8].

Decreased kidney function is associated with an increased risk of thromboembolic events [9–11] and is also regarded as a risk factor for bleeding complications during VKA treatment [8,12]. It has recently been reported that warfarin treatment is effective in preventing thromboembolic events when compared to aspirin in patients with atrial fibrillation and a moderate decrease in kidney function [13].

Creatinine and calculated glomerular filtration rate (eGFR) are two widely used markers of kidney function, but levels of creatinine depend critically on factors such as tubular secretion, drugs and dietary intake [14,15]. Cystatin C, a low molecular weight cysteine protease inhibitor, has been suggested as a better alternative to creatinine when evaluating renal function [16,17]. Previous studies have shown that cystatin C is a predictor of cardiovascular events and mortality in a non VKA treated population [18].

The primary aim of this study was to investigate the association between cystatin C, creatinine and eGFR and the risk of bleeding complications, cardiovascular events and all-cause mortality in patients treated with VKA.

Methods

We designed a longitudinal cohort study on a population with ongoing VKA treatment which has been described earlier [19]. In total, 719 patients with different indications for VKA treatment as described in Table 1, were recruited from the VKA clinics at Umeå University Hospital and Skellefteå County Hospital. Blood samples were collected at inclusion and patients were followed prospectively. Bleeding events, ischemic events and deaths were recorded and classified as described in the follow-up section. The study design is depicted in Fig. 1.

Abbreviations: CRP, C-reactive protein; eGFR, calculated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; INR, international normalized ratio; VKA, vitamin K antagonist; CV, coefficient of variance.

* Corresponding author at: Department of Medicine, Skellefteå County Hospital, 931 86 Skellefteå, Sweden. Tel.: +46 910771100; fax: +46 910771657.
E-mail address: Marcus.lind@vll.se (M. Lind).

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Table 1
Baseline data of the study cohort.

	Study cohort (n = 719)
Age at inclusion, mean (SD) years	70 (11)
Female, no. (%)	268 (37)
Follow-up time, mean (SD), years	4.2 (1.8)
Creatinine, meadian (IQR), μmol/L	79.6 (68.0-91.2)
Calculated glomerular filtration rate, median (IQR), mL/min/1.73 m2	77 (63.7-90.7)
Cystatin C, median (IQR), mg/L	0.97 (0.80-1.21)
CRP, median (IQR), mg/L	3.3 (1.62-6.62)
INR at baseline, n (%)*	
<2.0	33 (9)
2.0-3.5	303 (86)
>3.5	19 (5)
missing	1(0)
Indications for vitamin K antagonist treatment, no. (%)	
prosthetic heart valve	248 (35)
atrial fibrillation	228 (32)
venous thromboembolism	83 (11)
ischemic stroke	73 (10)
peripheral arterial thromboembolism	40(6)
miscellaneous	40 (6)
not defined	7(1)

Abbrevations: CRP- C-reactive protein. IQR – Inter Quartile Range.
* Available from the Skellefteå VKA-clinic.

Study Population

The study cohort was recruited from the VKA clinics at Skellefteå County Hospital, Skellefteå, Sweden, and Umeå University Hospital, Umeå, Sweden, in June of 1996. All patients received VKA treatment for at least 2 months prior to blood sampling. Out of the clinic population of 1204 patients, 957 were considered to be on long term treatment with VKA (more than 3 months of planned treatment) and were invited to participate in the study. Patients were excluded due to failure to answer the recruitment letter (n = 64), death or stopped treatment before sampling (n = 26), missing blood samples (n = 102) or declining to participate (n = 46). In the final study cohort 719 patients were included. Indications for treatment were obtained from documents at the VKA clinics.

Patients from the Skellefteå VKA clinic (n = 356) had additional data regarding clinical variables such as diabetes, prior peptic ulcer, prior bleeding peptic ulcer, and hypertension. Weight and height were obtained through questionnaires for patients and international normalized ratio (INR) was recorded at the time of study inclusion.

All patients gave informed consent according to the Declaration of Helsinki. The study was approved by the Research Ethics Committee of Umeå University.

Blood Sampling and Laboratory Procedures

At baseline, venous blood samples were drawn with a minimum of stasis and collected in standard siliconized, plasma tubes containing 0.13 mol/L sodium citrate. After centrifugation, the plasma samples were frozen and stored at – 70 ° C until analyzed. Samples were analyzed at the same time and location. The laboratory staff had no knowledge of event status.

C-reactive protein (CRP) was determined with an automated high sensitivity CRP method (IMMULITE Diagnostic Products Corporation, USA). The interassay CV was <6% in our hands. Creatinine was analysed on a Hitachii 911 multianalyser (Roche, Mannheim, Germany) with kits from Roche/Boehringer (Crea plus, enzymatic method). Cystatin C was measured by immunoparticle turbidimetry on a Hitachi 911 instrument, with reagents from DAKO, Copenhagen, Denmark.

eGFR was estimated by the four variable Modification of Diet in Renal Disease (MDRD) Study equation. (GFR = 175 x standardized Serum creatinine$^{-1.154}$ x age$^{-0.203}$ x 1.212 [if black] x 0.742 [if female]) [20]. INR was determined from the Owren-type prothrombin time at each hospital laboratory.

Follow–up

The date of blood sampling was set as the date of inclusion. The patients were followed longitudinally from June 1, 1996 until death, cessation of VKA treatment or January 1, 2002. All medical records from the Departments of Medicine, Surgery, Ear, Nose & Throat, Ophthalmology, Urology, Neurology, Neurosurgery and Orthopedic Surgery were reviewed during the study period. One patient relocated out of the region and was followed-up to the date of migration.

Bleeding complications, myocardial infarctions, ischemic strokes and peripheral arterial emboli were recorded and classified by a panel of three researchers (ML, JHJ, LJ). Major bleedings were defined according to International Society of Thrombosis and Haemostasis

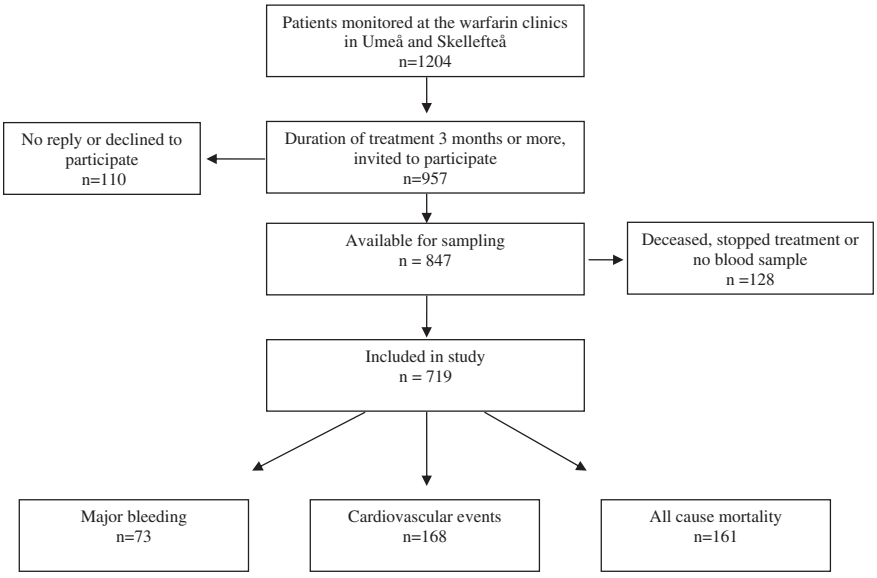

Fig. 1. Study population.