Chapter 5

Risk of venous thrombosis in patients with chronic kidney disease: Identification of high-risk groups

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ABSTRACT

Background: Although an association between venous thrombosis and chronic kidney disease has recently been established, it is unknown which patients with chronic kidney disease are most likely to benefit from thromboprophylaxis. The aim of this study was to assess the association between venous thrombosis and chronic kidney disease in combination with arterial thrombosis, malignancy, surgery, and thrombophilia to identify high-risk groups as a basis for personalized prevention.

Methods: This study included 2473 consecutive patients with first venous thrombosis and 2936 controls from a case-control study (the MEGA study).

Results: Moderately decreased kidney function (eGFR 30-60 ml/min) was associated with a 2.5-fold (95%CI 1.9-3.4) increased risk and severely decreased kidney function (eGFR <30 ml/min) was associated with a 5.5-fold (95%CI 1.8-16.7) increased risk, compared with those with normal kidney function (eGFR >90 ml/min). The risk of venous thrombosis was additionally increased for moderately and severely reduced kidney function in combination with arterial thrombosis (odds ratio 4.9; 95%CI 2.2-10.9), malignancy (5.8; 95%CI 2.8-12.1), surgery (14.0; 95%CI 5.0-39.4), immobilization (17.1; 95%CI 6.8-43.0), or thrombophilia (odds ratios 4.3-9.5), with particularly high risks when three or more risk factors were present (odds ratio 56.3; 95% CI 7.6-419.3).

Conclusion: Decreased kidney function is associated with an increased risk of venous thrombosis. The risk increased substantially in the presence of one or more other risk factors for thrombosis.

INTRODUCTION

Chronic kidney disease is an established risk factor for arterial thrombosis.[1-3] Until recently, it has been unclear whether chronic kidney diseases also increase the risk of venous thrombosis. In the Longitudinal Investigation of Thromboembolism Etiology (LITE) study, chronic kidney disease was associated with venous thrombosis in individuals older than 45 years of age.[4] This study reported that individuals with an estimated glomerular filtration rate between 15-60 ml/min had a 2.1-fold increased risk of venous thrombosis as compared with those with a normal kidney function. Recently, we confirmed these results in the Prevention of Renal and Vascular Disease (PREVEND) cohort study.[5] The moderately increased risk found in the above studies for chronic kidney disease probably does not justify the use of thromboprophylaxis when weighed against the thromboprophylaxis-related risk of major bleeding episodes.[6] Having chronic kidney disease in combination with other risk factors or high risk situations, such as immobilization, the presence of prothrombotic genes or other comorbidities, might increase the risk to such an extent that thromboprophylaxis would be recommendable. However, no studies have reported on the risk of venous thrombosis in persons with such combinations of risk factors.

We therefore calculated the estimated glomerular filtration rate in 2473 patients with a recent venous thrombosis and 2936 control subjects participating in a case-control (MEGA) study. The size of the study enabled us to investigate the risk for various glomerular filtration rates as well as the effects of combination with one or more other risk factors for thrombosis, with the aim of identifying high-risk groups that may benefit from thromboprophylaxis.

METHODS

Study design

The MEGA study (Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis study) is a large case-control study on risk factors for venous thrombosis. Between March 1999 and September 2004, consecutive patients aged 18 to 70 years with a first objectively confirmed episode of deep venous thrombosis (leg or arm) or pulmonary embolism were included from six participating anticoagulation clinics in the Netherlands. Information on the diagnostic procedure was obtained from hospital records and general practitioners.[7]

Patients

Only patients with a diagnosis of venous thrombosis that was confirmed with objective techniques were included in the analyses, as previously described.[7] Exclusion criteria were severe psychiatric problems and inability to speak Dutch. Of the 6567 eligible patients, 5184

participated (79%). For logistic reasons, blood sampling was performed for patients included up to June 2002.Therefore, in the current analyses 2473 patients out of the 5184 patients (48%) who had their blood drawn were included.

Controls

As control individuals, partners of patients aged <70 years without venous thrombosis were included, as well as individuals without venous thrombosis obtained via a random-digit-dialing (RDD) method. Of the 5184 participating patients, 3735 had an eligible partner. Of the 3735 eligible partners, 3039 participated (81%). The RDD control individuals were recruited from the same geographical area as the patients, and were frequency matched to the patients on age and sex. Of the 4350 eligible random controls, 2789 participated (64%). This resulted in a total of 5828 control individuals without venous thrombosis. Blood was drawn in participants included until June 2002, again for the same logistic reasons, which included 2936 control individuals (50%).

Data collection

All individuals were asked to complete an extensive questionnaire on many potential risk factors for venous thrombosis. Of particular interest for the current analysis are items on demographics (including age and sex), immobilization (defined as being bedridden for more than 4 days or hospitalization within 3 months prior to the index date), surgery within 3 months prior to the index date, history of arterial thrombosis (myocardial infarction, angina pectoris, ischemic stroke, transient ischemic attack, and peripheral vascular disease) (self-reported) and malignancy (validated for participating patients with cancer by reviewing discharge letters from their primary physician or from the hospital in which they were being treated).[8] The index date was the date of the thrombotic event for patients and their partners and the date of filling in the questionnaire for the random controls.

Laboratory assays

Approximately 3 months after discontinuation of oral anticoagulant therapy, thrombosis patients and their partners were invited for collection of a blood sample. In patients who were still on anticoagulant therapy 1 year after their event, blood was drawn during anticoagulant therapy. All assays were performed in an automated machine by laboratory technicians who were unaware of the case-control status of the samples. Serum creatinine was measured enzymatically (Roche Diagnostics, Mannheim, Germany). Glomerular filtration rate was estimated by the Modification of Diet in Renal Disease (MDRD) study equation.[9] Common genetic risk factors were assessed, including the factor V Leiden mutation and the prothrombin G20210A mutation, by polymerase chain reactions using the TaqMan assay.

Statistical analysis

To determine whether chronic kidney disease was associated with an increased risk for venous thrombosis, odds ratios (ORs) with 95% confidence intervals (95% CIs) adjusted for age and sex were calculated using unconditional logistic regression as estimates of the relative risk for mildly decreased kidney function (glomerular filtration rate 60-90 ml/min), moderately decreased kidney function (glomerular filtration rate 30-60 ml/min), and severely decreased kidney function (glomerular filtration rate <30 ml/min), as compared with normal kidney function. In our study, partner controls were matched on time to cases and random controls were selected from a stable, dynamic population.[10] We also investigated the association with venous thrombosis for glomerular filtration rate categories based on percentiles instead of using these clinical cut-off points for kidney function. In addition, odds ratios for venous thrombosis were calculated in order to identify high-risk groups, combining moderately to severely decreased kidney function (estimated glomerular filtration rate of <60 ml/min) with a priori specified risk factors (i.e. arterial thrombosis, malignancy, surgery, immobilization), and thrombophilia (factor V Leiden and prothrombin G20210A). As we were primarily interested in establishing high-risk groups that may benefit from thromboprophylaxis, we only adjusted for the matching factors, i.e. age and sex.[11,12] Adjusting for other factors when determining the association between chronic kidney disease and venous thrombosis is only of interest when determining the causal relationship. However, from a prediction point of view it is preferable to only determine the association between the predictive marker (chronic kidney disease) and the outcome (venous thrombosis), because adjustment could lead to false conclusions with respect to identifying high-risk groups. Statistical analyses were performed with statistical package SPSS Windows version 17.0 (SPSS Inc., Chicago, IL).

RESULTS

Table 1 shows the baseline characteristics of the study population. Of the 2473 thrombosis patients, 1473 (59.6%) had a deep vein thrombosis only and 1000 (40.4%) had a pulmonary embolism with or without deep vein thrombosis. Venous thrombosis patients had, as expected, more often arterial thrombosis, malignancy, surgery, immobilization, factor V Leiden mutation, or prothrombin G20210A than controls.

Table 1. Baseline characteristics

	Thrombosis patients N=2473		Controls N=2936	
Median age, years (5-95th %)	49.1	(25.9-67.5)	49.8	(27.1-67.0)
Women, n (%)	1346	(54.4%)	1543	(52.6%)
Arterial thrombosis, n (%)	147	(6.7%)	133	(4.8%)
Malignancy, n (%)	201	(8.2%)	107	(3.7%)
Surgery, n (%)	413	(16.7%)	85	(2.9%)
Immobilization, n (%)	663	(27.0%)	170	(5.8%)
Factor V Leiden, n (%)	390	(15.8%)	145	(4.9%)
Prothrombin G20210A, n (%)	117	(4.7%)	52	(1.8%)
Type of venous thrombosis, n (%)				
Deep vein thrombosis only	1473	(59.6%)		
Pulmonary embolism	1000	(40.4%)		

No major differences in mean glomerular filtration rates were observed when patients were tested on glomerular filtration rate within 3-6 months (mean 87 ml/min), 6-12 months (mean 86 ml/min), or >12 months (mean 86 ml/min) after their first venous thrombosis, suggesting that glomerular filtration rates were not influenced by a temporarily raised effect.

As shown in Table 2, the age- and sex-adjusted odds ratios of venous thrombosis increased with increasing severity of kidney disease compared with normal kidney function (glomerular filtration rate >90 ml/min): the odds ratio was 1.1 (95% CI 1.0-1.2) for mildly decreased kidney function (estimated glomerular filtration rate 60-90 ml/min), 2.5 (95% CI 1.9-3.4) for moderately decreased kidney function (estimated glomerular filtration rate 30-60 ml/min), and 5.5 (95% CI 1.8-16.7) for severely decreased kidney function (estimated glomerular filtration rate <30 ml/min). The odds ratios were similar for deep vein thrombosis and pulmonary embolism as separate outcomes.

When defining glomerular filtration rate categories based on percentiles instead of clinical cut-off points for kidney function, we also found, beside an increase in venous thrombosis risk with decreasing estimated glomerular filtration rate (Figure 1), an increased risk of venous thrombosis (odds ratio 1.4; 95% CI 1.0-1.9) for participants with glomerular hyperfiltration (i.e. those with the highest 2.5 percentile of the kidney function, corresponding to an estimated glomerular filtration rate of more than 125 ml/min).

To investigate joint effects of reduced kidney function and common risk factors for venous thrombosis, we categorized kidney function into two groups: reduced kidney function (moderately to severely decreased; estimated glomerular filtration rate <60 ml/min) and normal kidney function (estimated glomerular filtration rate 60-125 ml/min). Subjects with estimated

glomerular filtration rate of more than 125 ml/min were excluded from this analysis because their risk of venous thrombosis was also increased. Surgery in the absence of reduced kidney function increased the risk of venous thrombosis 6.9-fold (95% CI 5.3-8.8), while surgery combined with reduced kidney function increased the risk of venous thrombosis 14-fold (95% CI 5.0-39.4) (Table 3). Immobilization in the absence of reduced kidney function increased the risk of venous thrombosis 5.7-fold (95% CI 4.8-6.9), while immobilization combined with reduced kidney function increased the risk of venous thrombosis 17.1-fold (95% CI 6.8-43.0) (Table 3). The presence of all other risk factors, including malignancy, factor V Leiden mutation, or prothrombin G20210A, also additionally increased the risk for patients with reduced kidney function (Table 3).

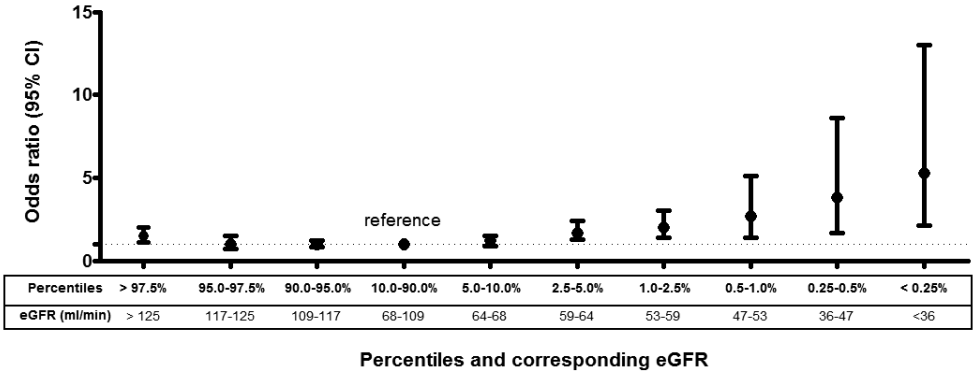

Figure 1. Percentiles of kidney function and risk of venous thrombosis

The risk of venous thrombosis further increased when more than one risk factor was present (Table 4). In the absence of immobilization, surgery, malignancy, arterial thrombosis, factor V Leiden, and prothrombin gene mutation, a reduced estimated glomerular filtration rate <60 ml/min was still associated with a two-fold increased risk of venous thrombosis (odds ratio 2.0, 95% CI 1.3-3.0). The presence of three or more of the six risk factors for venous thrombosis was associated with 56.3-fold (95% 7.6-419.3) increased risk of venous thrombosis.

There was a high risk of venous thrombosis for patients with chronic kidney disease patients with concomitant arterial thrombosis with surgery (odds ratio 17.9; 95% CI 2.2-146.2) or immobilization (odds ratio 16.8; 95% CI 3.8-75.1). In addition, chronic kidney disease patients with concomitant malignancy in combination with immobilization had a high risk of venous thrombosis (odds ratio 52.3; 95% CI 7.0-390.4). Also, the combination of chronic kidney disease with prothrombin G20210A or factor V Leiden in the presence of immobilization resulted in a high risk of venous thrombosis (odds ratio 17.8; 95% CI 4.0-78.7).

Table 2. Association between chronic kidney disease and venous thrombosis

eGFR (ml/min)	Description kidney function	Thrombosis Patients N	(%)	Controls N	(%)	Adjusted* odds ratio for venous thrombosis	Adjusted*† odds ratio for DVT	Adjusted*‡ odds ratio for PE
eGFR > 90	Normal	937	(37.9)	1179	(40.2)	1 (reference)	1 (reference)	1 (reference)
eGFR 60- 90	Mildly decreased	1376	(55.6)	1672	(56.9)	1.1 (1.0-1.2)	1.1 (0.9-1.2)	1.1 (1.0-1.3)
eGFR 30-60	Moderately decreased	144	(5.8)	81	(2.8)	2.5 (1.9-3.4)	2.2 (1.6-3.1)	2.9 (2.0-4.2)
eGFR < 30	Severely decreased	16	(0.6)	4	(0.1)	5.5 (1.8-16.7)	7.0 (2.2-21.8)	3.4 (0.8-13.7)

*Adjusted for age and sex; †DVT, deep vein thrombosis only; ‡PE, pulmonary embolism with or without deep vein thrombosis

Table 3. Joint effects on venous thrombosis of chronic kidney disease and surgery, immobilization, malignancy, factor V Leiden, and prothrombin G20210A

Decreased kidney function*	Acquired or genetic risk factor	Thrombosis patients		Controls		Adjusted† odds ratio (95% CI)	
		N	(%)	N	(%)		
	Arterial thrombosis						
No	No	1878	(87.8)	2524	(92.4)	1	(reference)
Yes	No	114	(5.3)	75	(2.7)	2.2	(1.6-3.0)
No	Yes	120	(5.6)	124	(4.5)	1.4	(1.1-1.8)
Yes	Yes	26	(1.2)	8	(0.3)	4.9	(2.2-10.9)
	Malignancy						
No	No	2053	(86.6)	2674	(93.6)	1	(reference)
Yes	No	124	(5.2)	76	(2.7)	2.3	(1.7-3.1)
No	Yes	159	(6.7)	98	(3.4)	2.3	(1.8-3.0)
Yes	Yes	36	(1.5)	9	(0.3)	5.8	(2.8-12.1)
	Surgery						
No	No	1845	(72.8)	2681	(94.3)	1	(reference)
Yes	No	124	(4.4)	79	(2.8)	2.4	(1.8-3.3)
No	Yes	366	(20.6)	78	(2.7)	6.9	(5.3-8.8)
Yes	Yes	36	(2.2)	4	(0.1)	14.0	(5.0-39.4)
	Immobilization						
No	No	1633	(68.9)	2600	(91.5)	1	(reference)
Yes	No	107	(4.5)	76	(2.7)	2.3	(1.7-3.2)
No	Yes	579	(24.4)	160	(5.6)	5.7	(4.8-6.9)
Yes	Yes	52	(2.2)	5	(0.2)	17.1	(6.8-43.0)
	Factor V Leiden						
No	No	1871	(78.4)	2642	(92.3)	1	(reference)
Yes	No	136	(5.7)	77	(2.7)	2.6	(2.0-3.5)
No	Yes	358	(15.0)	134	(4.7)	3.8	(3.1-4.6)
Yes	Yes	23	(1.0)	8	(0.3)	4.3	(1.9-9.7)
	Prothrombin G20210A						
No	No	2120	(88.8)	2726	(95.3)	1	(reference)
Yes	No	152	(6.4)	84	(2.9)	2.5	(1.9-3.3)
No	Yes	109	(4.6)	50	(1.7)	2.8	(2.0-3.9)
Yes	Yes	7	(0.3)	1	(0.0)	9.5	(1.2-77.4)

*Decreased kidney function defined as eGFR<60 ml/min as compared with eGFR 60-125 ml/min; †Adjusted for age and sex

Table 4. Odds ratios for venous thrombosis for total number of risk factors present per person

Chronic kidney disease*	Number of genetic/acquired risk factors†	Age and sex adjusted odds ratio (95% CI)
No	0	1 (reference)
Yes	0	2.0 (1.3-3.0)
No	1	3.2 (2.8-3.7)
Yes	1	7.8 (4.4-13.8)
No	2	9.6 (7.3-12.5)
Yes	2	7.6 (3.0-19.2)
No	≥ 3	13.2 (7.7-22.6)
Yes	≥ 3	56.3 (7.6-419.3)

*Chronic kidney disease eGFR<60ml/min (Yes) as compared with eGFR 60-125 ml/min; †Risk factors: arterial thrombosis, malignancy, surgery, immobilization, factor V Leiden, or prothrombin G20210A

DISCUSSION

In this large case-control study, kidney function showed an inverse association with venous thrombosis risk with a nearly 6-fold increased risk for those with severely decreased kidney function (estimated glomerular filtration rate <30 ml/min). Those with additional risk factors had an even higher risk of thrombosis, particularly patients who were immobilized or underwent surgery (around 15-fold increased risk). Furthermore, there was a cumulative effect when several risk factors were present simultaneously with renal function impairment, with up to 56-fold increased risks. Since these involve common medical circumstances, these findings may offer a tool for targeted thromboprophylaxis in vulnerable patients.

In line with our results, both the LITE[4] and PREVEND[5] study found an increased risk of venous thrombosis for chronic kidney disease. Interestingly, we showed that a high glomerular filtration rate of more than 125 ml/min was also associated with an increased risk of venous thrombosis (odds ratio 1.4; 95% CI 1.0-1.9). A high glomerular filtration rate has been shown to be an indicator for early kidney disease and a predictor of cardiovascular disease.[13-16]

Based on the odds ratios of venous thrombosis for decreased kidney function ranging from 1.1 for mildly decreased kidney function (estimated glomerular filtration rate 60-90 ml/min) to 5.5 for severely decreased kidney function (estimated glomerular filtration rate <30 ml/min), thromboprophylaxis is probably not justified in all patients with decreased kidney function since it does not seem to outweigh the increased bleeding risk associated with decreased kidney function.[17,18] However, our data imply that chronic kidney disease is especially relevant when it is present in combination with other risk factors for venous thrombosis, because we found a 4- to 17-fold increased risk when chronic kidney disease was jointly present with arterial thrombosis, malignancy, surgery, immobilization, factor V Leiden, or prothrombin G20210A.

The risk of venous thrombosis was 56.3-fold increased in the presence of chronic kidney disease and three or more of the six risk factors (arterial thrombosis, malignancy, surgery, immobilization, factor V Leiden, and prothrombin G20210A). These observations could have clinical implications. The American College of Chest Physicians (ACCP) currently recommends pharmacologic thromboprophylaxis for several hospitalized groups at high risk for venous thrombosis, including patients with a major trauma, spinal cord injury, or heart failure,[6] but not including patients with chronic kidney disease. Our study results suggest, however, that these patients are also at increased risk of venous thrombosis, especially in combination with one or more other risk factors. In patients with arterial thrombosis or malignancy who are immobilized or will undergo surgery, creatinine measurements are often routinely performed (for example before diagnostic testing with contrast agents, for medication dosing, or to identify concurrent kidney damage) and can therefore be easily taken into account when deciding on thrombosis prophylaxis. However, a potential problem in patients with a chronic kidney disease is the increased bleeding risk associated with anticoagulation use.[17,18] Therefore, each person's risks and benefits need to be weighed individually until there are randomized clinical trials answering these questions. Furthermore, screening for thrombophilia in patients with chronic kidney disease is probably not justified given the low prevalence of thrombophilia (factor V Leiden and prothrombin gene mutation) and given the moderately increased risks of venous thrombosis.

Decreased glomerular filtration has been associated with endothelial dysfunction and subsequent arterial thrombosis.[1-3,19] Endothelial dysfunction has also been associated with changes in the levels of several coagulation proteins and with an increased venous thrombosis risk.[20] Hence, in theory, the association between chronic kidney disease and venous thrombosis could be causally explained through endothelial dysfunction. However, these assumptions are merely based on literature,[21] and we did not assess endothelial dysfunction in this study. Addressing the mechanism through which chronic kidney disease increases the risk of venous thrombosis was not the aim of this study, as we were primarily interested in establishing high-risk groups that may benefit from thromboprophylaxis, irrespective of the underlying causal relation. Research into this relation has yet to be conducted.

A limitation of this study is that we had no information about proteinuria. It would be useful to explore whether proteinuria in combination with decreased kidney function is associated with a more increased risk of venous thrombosis than decreased kidney function alone. Proteinuria, especially in the nephrotic range, has been associated with venous thrombosis.[22-24] Another limitation was that arterial thrombosis was self-reported. However, we expect that patients and control persons misreported arterial thrombosis similarly and infrequently, because these are major diseases with a large impact limiting recall bias. Random misclassification would

result in an underestimation of our odds ratios. Of note, we used the cut-off levels for the glomerular filtration rate of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines to define kidney disease.[25] Nevertheless, it would have been interesting to identify risk of venous thrombosis in, for example, kidney-transplanted patients or patients who had hemodialysis or peritoneal dialysis treatment, but this information was not available in our study. Strengths of this study include the large patient sample and detailed information about other risk factors for venous thrombosis such as history of arterial thrombosis, malignancy, surgery, immobilization, and genetic risk factors. Nevertheless in some subgroups numbers became small, which may have led to slightly inflated risk estimates.

In summary, in a large case-control population we found that a decreasing kidney function was associated with an increasing risk of venous thrombosis. The risk of venous thrombosis in individuals with chronic kidney disease was further increased in the presence of additional risk factors for venous thrombosis. These high-risk groups could be considered for future intervention trials into the effectiveness of thromboprophylaxis.

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