Chapter 2

Risk of venous thrombosis in patients with major illnesses: Results from the MEGA study

Gürbey Ocak
Carla Y. Vossen
Marion Verduijn
Friedo W. Dekker
Frits R. Rosendaal
Suzanne C. Cannegieter
Willem M. Lijfering

J Thromb Haemost. 2013; 11(1): 116-123

ABSTRACT

Background: The risk of venous thrombosis associated with major illnesses is not well known, as is the combined effect of immobilization, and thrombophilia. The aim of this study was to assess the effect on the development of venous thrombosis of several major illnesses in combination with immobilization, BMI, and thrombophilia to identify high-risk groups that may provide a basis for personalized prevention.

Methods: This study included 4311 consecutive patients with a first episode of venous thrombosis and 5768 controls from a case-control study (MEGA study). We calculated odds ratios (ORs) for venous thrombosis for patients with a self-reported history of major illnesses.

Results: Venous thrombosis risk was increased for all investigated major illnesses: liver disease (OR) 1.7 (95%CI 1.0-2.9), kidney disease 3.7 (95%CI 2.3-5.9), rheumatoid arthritis 1.5 (95%CI 1.2-1.9), multiple sclerosis 2.4 (95%CI 1.3-4.3), heart failure 1.7 (95%CI 1.2-2.3), hemorrhagic stroke 4.9 (95%CI 2.4-9.9), arterial thrombosis 1.5 (95%CI 1.2-1.8), and in the presence of any of the above major illnesses 1.7 (95%CI 1.5-1.9). Combinations of major illnesses with immobilization and increased factor VIII (odds ratio 79.9; 95%CI 33.2-192.2), increased factor IX (35.3; 95%CI 14.2-87.8), increased von Willebrand factor (88.0; 95%CI 33.9-228.3), factor V Leiden (84.2; 95%CI 19.5-363.6), and blood group non-O (53.1; 95%CI 30.9-91.4) were associated with increased venous thrombosis risks.

Conclusion*:* All major illnesses reported here were associated with an increased risk of venous thrombosis. These risks were most pronounced at time of immobilization or in the presence of thrombophilia.

INTRODUCTION

Venous thrombosis occurs in 1-2 per 1000 persons annually.[1] Although venous thrombosis is a preventable disease, only a few provoking risk factors, such as surgery and hospitalization, are currently considered harmful enough to warrant prophylactic measures.[2]

A number of studies have reported on the risk of venous thrombosis in patients with a history of major illnesses including liver disease,[3-5] kidney disease,[6-9] rheumatoid arthritis,[4,10] multiple sclerosis,[11] heart failure,[4,12,13] hemorrhagic stroke,[14] and arterial thrombosis.[4,15-18] Some of these studies found a positive association between major illnesses and venous thrombosis,[4-15,18] whereas other studies did not.[3,16,17] The use of different definitions of major illnesses, together with variation in the studied populations, may explain this discrepancy. Studies on the association between kidney disease and venous thrombosis,[6-9] however, found consistent increased risks of venous thrombosis ranging from a 1.3-fold increased risk for patients with a mildly decreased kidney function[9] to an 8-fold in increased risk for patients with a nephrotic syndrome.[6] Even if these major illnesses were to be considered as risk factors for venous thrombosis, the risk may not be sufficiently high to justify the use of prophylaxis in all these situations, due to the increased risk of bleeding associated with most prophylactic measures (i.e. anticoagulant therapy).[19] The risk-benefit ratio may favor the use of such prophylactic measures only in persons at particularly increased risk of venous thrombosis. Patients with a major illness in combination with other risk factors, like immobilization or thrombophilia, who have high risks of venous thrombosis could benefit from prophylaxis during periods of high risks. Thus far, no studies have reported on the risk for venous thrombosis in persons with such combinations of prothrombotic conditions. Nor are there studies available that calculated the risk for venous thrombosis in patients with a major illness who are immobilized or have a genetic or acquired thrombophilia, such as factor (F) V Leiden or elevated levels of factor (F) VIII.

The aim of our study was to investigate the association between major illnesses (liver disease, kidney disease, rheumatoid arthritis, multiple sclerosis, heart failure, hemorrhagic stroke, and arterial thrombosis) and risk of venous thrombosis.

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, of which details have been published previously.[20,21] In brief, between March 1999 and September

2004, consecutive patients aged 18 to 70 years with a first objectively confirmed episode of deep venous thrombosis 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.

Patients

Only patients with a diagnosis of venous thrombosis that was confirmed with objective techniques were included in the analyses.[20,21] Exclusion criteria were severe psychiatric problems and inability to speak Dutch. Of the 6567 eligible patients, 5184 participated (79%). For the present analysis, questionnaire data on major illnesses were available from 4311 patients and 5768 controls, after exclusion of patients with a deep vein thrombosis of the arm (n=227).

Controls

As control persons, partners of patients aged <70 years without venous thrombosis were included, as well as persons 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, 2979 participated (80%) and completed a questionnaire including questions about the presence of major illnesses. The RDD control persons 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, four died before they were able to participate. Of the remaining 4346 individuals, 3000 participated (69%). Of the nonparticipants, 15 were in the end stage of disease and 1331 refused to participate or could not be located. A questionnaire was returned by 2789 of the participating random controls. This resulted in a total of 5768 control persons without venous thrombosis.

Data collection

All persons were asked to complete an extensive questionnaire on many potential risk factors for venous thrombosis. Of particular interest for this study question are items on general health characteristics (age, sex, body weight, height, and immobilization (defined as bedridden at home for at least 4 days, hospitalization, or surgery within three months prior to the index date)). Body mass index was calculated by dividing self-reported body weight (kg) by squared self-reported height (m^2). 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. The questionnaire also included questions about the presence of liver disease, kidney disease, rheumatoid arthritis, multiple sclerosis, heart failure, hemorrhagic stroke, and arterial thrombosis (myocardial infarction, angina, ischemic stroke, transient ischemic attack, and peripheral vascular disease) in the medical history.

Blood collection

Approximately 3 months after discontinuation of oral anticoagulant therapy, 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 by automated coagulation assays by laboratory technicians who were unaware of the case-control status of the samples. For logistic reasons, blood sampling was performed for patients up to June 2002; after this date only DNA was collected via buccal swabs. Plasma samples were available for 2134 of 4311 (50%) cases and 2812 of 5768 (49%) control persons. Since we stopped taking blood after June 2002 for logistic reasons only, this could not have introduced bias. FVIII activity was measured with a mechanical clot detection method on a STA-R coagulation analyzer following the instructions of the manufacturer (Diagnostica Stago, Asnieres, France). Levels of FIX antigen were determined by enzyme-linked immunosorbent assay (ELISA). Von Willebrand factor (VWF) antigen was measured with the immunoturbidimetric method, using the STA Liatest kit (rabbit anti–human VWF antibodies), following the instructions of the manufacturer (Diagnostica Stago).[21,22] The mean intra-assay and inter-assay coefficients of variation were 3.7% and 8.9% for factor VIII activity levels, respectively, 4.3% and 2.7% for factor IX antigen levels, respectively, and 3.6% and 2.6% for von Willebrand factor antigen levels, respectively.

DNA samples were available for 3957 of 4311 (92%) cases and 4680 of 5768 (81%) control persons. Common genetic risk factors were assessed, including the FV Leiden mutation and ABO-blood group, by polymerase chain reactions using the TaqMan assay.[21] To genotype ABO-blood group, we determined the 20146G/- (rs8176719), 21463C/G (rs7853989), 21867A/G (rs8176749), and 21996C/- (rs8176750) blood group polymorphisms by a 5'nuclease assay (Taqman; Applied Biosystems, Foster City, CA, USA) using a standard PCR reaction mix (Eurogentec, Seraing, Belgium) and an allele-specific fluorescent probe equipped with a minorgroove binding moiety (Applied Biosystems). FV Leiden and blood group non-O, and increased levels of VWF, FVIII, and FIX were specifically chosen as thrombophilic conditions, because these are either prevalent genetic risk factors, or coagulation factors associated with highest venous thrombosis risks.[23]

Statistical analysis

To determine whether the presence of one or more major illnesses was associated with an increased risk for venous thrombosis as compared with persons without a major illness, odds ratios with 95% confidence intervals (95% CIs) adjusted for age and sex (the matching factors) were calculated. We made cut-off points for FVIII (155 IU/dL), FIX (119 IU/dL), and VWF levels (142 IU/dL) that correspond with the 80th percentiles in the control population. Persons who were using anticoagulant therapy at time of blood collection were excluded from the analysis

of the effect of vitamin K–dependent coagulation FIX. Odds ratios for venous thrombosis were calculated for the combination of major illness and immobilization, increased body mass index (≥25 kg/m^2), or thrombophilia (FV Leiden, non-O blood group, and elevated levels of FVIII, FIX, and VWF) to identify high-risk groups that could benefit from thromboprophylaxis. Addressing the causal relation between major illness and risk of venous thrombosis was not the aim of this study.[22] Therefore, we only adjusted for the matching factors, i.e. age and sex.[24] Malignancy was not considered as a major illness as a previous report of the MEGA study already published about malignancy and risk of venous thrombosis.[21] Statistical analyses were performed with statistical package SPSS Windows version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics

4311 patients with venous thrombosis and 5768 control persons without venous thrombosis were included in the current analysis. Table 1 shows the general characteristics of the study population. Of the patients, 2477 (57%) had a deep vein thrombosis of the leg only, and 1834 (43%) had a pulmonary embolism with or without deep vein thrombosis. Patients, as expected, had a higher BMI, were more often immobilized, were more likely to have FV Leiden and non-O blood group, and had higher levels of coagulation factors than control persons.

Odds ratios for venous thrombosis

Odds ratios for venous thrombosis associated with major illnesses all pointed in the same direction and were of similar magnitude, regardless of whether partners or RDD control persons were used as the control group (Table 2). Therefore, we combined these control groups for the further analyses. The prevalence of a history of a major illness was 14% in patients and 8% in controls. Presence of liver disease (odds ratio 1.7; 95% CI 1.0-2.9), rheumatoid arthritis (odds ratio 1.5; 95% CI 1.2-1.9), heart failure (odds ratio 1.7; 95% CI 1.2-2.3), and arterial thrombosis (odds ratio 1.5; 95% CI 1.2-1.8) were associated with an increased risk of venous thrombosis after adjustment for age and sex. Kidney disease (odds ratio 3.7; 95% CI 2.3-5.9), history of hemorrhagic stroke (odds ratio 4.9; 95% CI 2.4-9.9), and multiple sclerosis (odds ratio 2.4; 95% CI 1.3-4.3) were also associated with an increased risk of venous thrombosis.

Table 1. Baseline characteristics

	Thrombosis patients N= 4311		Partner controls N= 2979		RDD controls N= 2789		Partner and RDD controls N= 5768	
Median age, years (5-95th %)	49.7	(25.9-67.8)	50.4	(28.0-66.4)	45.5	(23.3-67.0)	48.1	(25.4-66.7)
Women, N (%)	2326	(54.0)	1517	(50.9)	1593	(57.1)	3110	(53.9)
Median BMI, kg/m^2, (5-95th %)	26.2	(20.1-35.5)	25.5	(20.3-33.7)	24.5	(19.6-32.5)	25.0	(19.9-33.1)
Immobilization*, N (%)	1662	(38.6)	440	(14.8)	507	(18.2)	947	(16.4)
Thrombophilia								
Factor V Leiden, N (%)	626	(15.8)	143	(5.4)	109	(5.4)	252	(5.4)
Blood group non-O, N (%)	2804	(71.2)	1429	(53.6)	1094	(54.5)	2523	(53.9)
Median factor VIII, IU/dL (5-95th %)	154	(83-280)	116	(65-212)	113	(65-200)	114	(65-208)
Median factor IX, IU/dL (5-95th %)	108	(80-144)	105	(78-139)	102	(76-135)	103	(77-137)
Median VWF, IU/dL (5-95th %)	138	(75-255)	105	(57-196)	103	(57-186)	105	(57-191)

RDD, random digit dialing; BMI, body mass index. *Defined as bedridden for more than 4 days, surgery, or hospitalization within 12 months prior to the index date

Table 2. Association between major illnesses and the risk of venous thrombosis

	Patients	Controls	Adjusted odds ratios* (95% confidence interval)				
	N	N	Overall	Partner controls	RDD controls	Deep vein thrombosis	Pulmonary embolism†
Major illness							
No	3720	5290	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Yes	591	478	1.7 (1.5-1.9)	1.7 (1.5-2.0)	1.6 (1.3-1.9)	1.4 (1.2-1.7)	2.0 (1.7-2.4)
Liver disease	27	22	1.7 (1.0-2.9)	1.8 (0.9-3.7)	1.5 (0.7-3.0)	1.7 (0.9-3.2)	1.6 (0.8-3.3)
Kidney disease	60	23	3.7 (2.3-5.9)	4.1 (2.2-7.9)	3.4 (1.8-6.3)	3.3 (1.9-5.6)	4.2 (2.4-7.2)
Rheumatoid arthritis	145	132	1.5 (1.2-1.9)	1.4 (1.1-1.9)	1.5 (1.1-2.1)	1.3 (1.0-1.8)	1.7 (1.2-2.2)
Multiple sclerosis	30	17	2.4 (1.3-4.3)	4.3 (1.7-11.0)	1.5 (0.8-3.0)	2.6 (1.3-5.0)	2.1 (1.0-4.4)
Heart failure	76	60	1.7 (1.2-2.3)	2.0 (1.3-3.2)	1.3 (0.9-2.0)	1.1 (0.7-1.7)	2.5 (1.7-3.6)
Hemorrhagic stroke	36	10	4.9 (2.4-9.9)	4.6 (1.9-10.9)	5.5 (2.0-15.6)	4.8 (2.2-10.1)	5.0 (2.2-11.2)
Arterial thrombosis	299	264	1.5 (1.2-1.8)	1.6 (1.3-1.9)	1.4 (1.1-1.8)	1.1 (0.9-1.4)	2.0 (1.6-2.4)
MI	137	116	1.5 (1.2-2.0)	1.7 (1.3-2.3)	1.4 (1.0-1.9)	0.9 (0.6-1.3)	2.5 (1.8-3.3)
Angina	64	49	1.7 (1.1-2.4)	1.5 (1.0-2.3)	2.0 (1.2-3.4)	1.1 (0.7-1.8)	2.4 (1.6-3.8)
Ischemic stroke	41	38	1.4 (0.9-2.3)	1.6 (0.9-2.7)	1.3 (0.8-2.3)	1.4 (0.8-2.3)	1.5 (0.9-2.7)
TIA	61	58	1.4 (1.0-2.0)	1.4 (0.9-2.1)	1.4 (0.8-2.2)	1.2 (0.8-1.9)	1.6 (1.0-2.4)
PVD	55	52	1.4 (0.9-2.0)	1.5 (0.9-2.3)	1.3 (0.8-2.1)	1.4 (0.9-2.2)	1.3 (0.8-2.2)

MI, myocardial infarction; TIA, transient ischemic attack; PVD, peripheral vascular disease. *Adjusted for age and sex. †Pulmonary embolism with or without deep vein thrombosis

Odds ratios for deep vein thrombosis and pulmonary embolism

As shown by the point estimates, the odds ratios for deep vein thrombosis alone were higher than the odds ratios for pulmonary embolism with or without deep vein thrombosis in patients with liver disease and multiple sclerosis. All other major illnesses yielded a similar or lower odds ratio for deep vein thrombosis alone than for pulmonary embolism with or without deep vein thrombosis.

Combined major illnesses

The odds ratio of venous thrombosis was 2.2 (95% CI 1.5-3.1) in the presence of two or more major illnesses and was 1.6 (95% CI 1.4-1.8) in the presence of only one major illness as compared to the absence of a major illness.

Immobilization, body mass index and thrombophilia

In Table 3, the combined effects of immobilization, increased body mass index (≥25 kg/m^2) or thrombophilia with major illnesses on venous thrombotic risk are shown. The odds ratio for immobilization in the absence of major illnesses was 6.2 (95% CI 5.4-7.0). The combination of immobilization with a major illness yielded an odds ratio of 10.4 (95% CI 7.5-14.4). Participants with liver disease, kidney disease, rheumatoid arthritis, and arterial thrombosis had odds ratios in combination with immobilization of 8.3 (95% CI 2.8-24.4), 31.7 (95% CI 7.6-132.1), 11.7 (95% CI 5.8-23.6) and 11.6 (95% CI 7.1-19.2), respectively. The odds ratio of venous thrombosis for a major illness was 2.3 (95% CI 1.9-2.9) in the absence of an increased body mass index and 2.3 (95% CI 2.0-2.8) in the presence of an increased body mass index. The odds ratio of venous thrombosis for a major illness was 1.7 (95% CI 1.5-2.0) without FV Leiden and 4.0 (95% CI 2.5-6.5) in FV Leiden carriers. The odds ratio of venous thrombosis for a major illness in the presence of blood group non-O was 3.3 (95% CI 2.7-4.0) and the odds ratio in the absence of blood group non-O was 1.9 (95% CI 1.5-2.4). A major illness combined with a normal level of FVIII, FIX, or VWF led to odds ratios of 1.6 (95% 1.2-2.1), 1.4 (95% 1.1-1.8), and 1.6 (95% 1.2-2.0), respectively. These odds ratios were 5.5 (95% CI 4.1-7.3), 2.3 (95% CI 1.7-3.2), and 5.4 (95% CI 4.1-7.3) in the presence of elevated levels of FVIII, FIX, or VWF, respectively. Participants with multiple sclerosis in combination with increased FVIII levels had a high risk of venous thrombosis (odds ratio 12.5; 95% CI 1.5-107.9), as did participants with arterial thrombosis and increased FVIII levels (odds ratio 5.5; 95% CI 3.8-8.0).

Table 3. Combined effect of established risk factors for venous thrombosis and major illnesses on venous thrombosis risk

Major illness	Risk factor	Immobilization		BMI ≥25 kg/m^2		Factor V Leiden		Blood group non-O		FVIII		FIX		VWF	
		OR*	(95% CI)	OR*	(95% CI)	OR*	(95% CI)	OR*	(95% CI)	OR*	(95% CI)	OR*	(95% CI)	OR*	(95% CI)
No major illness	No risk factor	1	(ref)	1	(ref)	1	(ref)	1	(ref)	1	(ref)	1	(ref)	1	(ref)
Major illness	No risk factor	1.3	(1.2-1.6)	2.3	(1.9-2.9)	1.7	(1.5-2.0)	1.9	(1.5-2.4)	1.6	(1.2-2.1)	1.4	(1.1-1.8)	1.6	(1.2-2.0)
No major illness	Risk factor	6.2	(5.4-7.0)	1.7	(1.5-1.8)	3.5	(3.0-4.1)	2.2	(2.0-2.4)	4.5	(3.9-5.2)	1.6	(1.4-1.9)	4.2	(3.7-4.8)
Major illness	Risk factor	10.4	(7.5-14.4)	2.3	(2.0-2.8)	4.0	(2.5-6.5)	3.3	(2.7-4.0)	5.5	(4.1-7.3)	2.3	(1.7-3.2)	5.4	(4.1-7.3)
Liver disease	No risk factor	0.9	(0.4-2.0)	2.8	(1.1-6.8)	1.6	(0.8-3.1)	4.1	(1.0-16.3)	1.5	(0.3-6.9)	1.3	(0.5-3.4)	0.6	(0.1-2.9)
	Risk factor	8.3	(2.8-24.4)	2.0	(0.9-4.6)	5.9	(0.7-52.6)	2.2	(1.0-4.5)	4.5	(1.8-11.6)	11.0	(1.3-91.5)	8.0	(2.6-24.7)
Kidney disease	No risk factor	2.1	(1.2-3.9)	5.0	(2.3-10.8)	3.6	(2.1-6.1)	3.8	(1.8-7.9)	2.8	(0.9-8.4)	1.8	(0.8-4.4)	1.8	(0.8-4.5)
	Risk factor	31.7	(7.6-132.1)	4.9	(2.6-9.1)	4.3	(0.9-21.4)	7.0	(3.4-14.1)	3.9	(1.7-9.0)	1.8	(0.5-6.2)	7.2	(2.3-22.3)
Rheumatoid arthritis	No risk factor	1.2	(0.9-1.6)	2.1	(1.5-3.1)	1.5	(1.2-2.0)	2.1	(1.4-3.1)	1.2	(0.7-2.1)	1.2	(0.8-2.0)	1.4	(0.8-2.2)
	Risk factor	11.7	(5.8-23.6)	1.8	(1.3-2.6)	3.0	(1.3-7.5)	2.6	(1.8-3.7)	5.1	(3.0-8.7)	2.2	(1.2-4.0)	4.8	(2.8-8.3)
Multiple sclerosis	No risk factor	2.5	(1.2-5.5)	2.0	(0.8-4.9)	2.6	(1.4-5.1)	2.7	(1.0-6.8)	2.1	(0.7-5.7)	1.7	(0.6-5.0)	2.3	(0.8-6.6)
	Risk factor	4.3	(1.6-11.2)	5.1	(2.2-12.2)	1.3	(0.1-20.4)	4.8	(2.0-11.6)	12.5	(1.5-107.9)	4.6	(0.9-23.6)	5.8	(1.1-29.9)
Heart failure	No risk factor	1.7	(1.1-2.5)	2.9	(1.6-5.2)	1.8	(1.2-2.6)	1.6	(0.9-2.9)	1.6	(0.8-3.2)	1.1	(0.5-2.3)	1.7	(0.9-3.3)
	Risk factor	4.6	(2.3-9.2)	2.0	(1.3-3.1)	2.0	(0.3-12.2)	3.5	(2.2-5.7)	6.9	(3.2-15.1)	2.3	(0.9-5.8)	6.7	(3.0-15.3)
Hemorrhagic stroke	No risk factor	3.3	(1.5-7.2)	12.8	(2.9-56.3)	4.6	(2.2-9.8)	1.4	(0.5-4.5)	7.6	(2.1-28.4)	4.1	(1.3-13.5)	5.9	(1.8-19.0)
	Risk factor	Not estimable		5.9	(2.5-13.9)	Not estimable		26.5	(6.3-112.1)	6.7	(1.8-25.5)	6.9	(0.8-61.6)	8.6	(1.8-41.9)
Arterial thrombosis	No risk factor	1.2	(1.0-1.5)	2.0	(1.5-2.8)	1.5	(1.2-2.8)	1.7	(1.3-2.3)	1.6	(1.2-2.3)	1.6	(1.1-2.3)	1.6	(1.2-2.3)
	Risk factor	11.6	(7.1-19.2)	2.2	(1.7-2.7)	5.2	(2.6-10.5)	3.0	(2.3-3.8)	5.5	(3.8-8.0)	2.2	(1.4-3.3)	5.0	(3.4-7.2)

OR, odds ratio; VWF, von Willebrand factor. *Odds ratio adjusted for age and sex. Thrombophilia defined as levels elevated above the 80th percentiles of the control group: FVIII levels >155 IU/dL, FIX >119 IU/dL, and VWF >142 IU/dL

Combinations of a major illness with immobilization and increased FVIII levels (odds ratio 79.9; 95% CI 33.2-192.2), increased FIX levels (odds ratio 35.3; 95% CI 14.2-87.8), increased VWF levels (odds ratio 88.0; 95% CI 33.9-228.3), FV Leiden (odds ratio 84.2; 95% CI 19.5-363.6), and blood group non-O (odds ratio 53.1; 95% CI 30.9-91.4) were associated with the highest venous thrombosis risks (Table 4).

Table 4. Odds ratios for venous thrombosis for combinations of risk factors

Major illness	Immobilization	Thrombophilia*	Age and sex adjusted odds ratio (95% CI)
No major illness	No immobilization	No Thrombophilia	1 (ref)
Any major illness	+ immobilization	No Thrombophilia	10.9 (4.2-28.2)
Any major illness	+ immobilization	+ increased FVIII levels	79.9 (33.2-192.2)
Any major illness	+ immobilization	+ increased FIX levels	35.3 (14.2-87.8)
Any major illness	+ immobilization	+ increased VWF levels	88.0 (33.9-228.3)
Any major illness	+ immobilization	+ factor V Leiden	84.2 (19.5-363.6)
Any major illness	+ immobilization	+ blood group non-O	53.1 (30.9-91.4)

*No thrombophilia defined as the absence of increased FVIII levels (>155 IU/dL), increased FIX levels (>119 IU/dL), increased VWF levels (>142 IU/dL), factor V Leiden, and blood group non-O.

DISCUSSION

In this large case-control study, major illnesses were associated with an overall 1.7-fold (95% CI 1.5-1.9) increased risk of venous thrombosis, varying from a 1.4-fold increased risk for a history of ischemic stroke, transient ischemic attacks and peripheral vascular disease to a 4.9-fold increased risk for hemorrhagic stroke. Overall, odds ratios were slightly higher for pulmonary embolism with or without deep vein thrombosis than for deep vein thrombosis alone. Major illnesses were associated with higher risks of venous thrombosis when the patient was additionally immobilized and had thrombophilia. This was not the case for the combination of a major illness with an increased body mass index.

The reason for performing this study was to explore whether risk groups could be identified that would benefit from targeted prevention of venous thrombosis with pharmacological agents. Therefore, we were not interested in the causal relation between major illnesses and venous thrombosis, i.e. we did not adjust for potential confounding factors. From a prediction point of view, it is not important whether a major illness has a causal relation with venous thrombosis, since these patients could be targeted for thromboprophylaxis if there is a high risk of venous thrombosis irrespective of whether a causal relation exists or not.[22]

On the whole, based on the point estimates, our study suggests that the risk of venous thrombosis was increased when more major illnesses were present or when a major illness was present in combination with immobilization and thrombophilia. This is in line with the concept of venous thrombosis as a multicausal disease.[25] The presence of more major illnesses could have increased coagulation factor levels in MEGA participants. In addition, immobilization may be a good marker for severity of disease. As we had no information on disease severity, we could not investigate whether the underlying major illness itself, or immobilization associated with major illness, increased the risk of venous thrombosis. However, for prediction of high-risk groups, the causal path leading to venous thrombosis is not important as, either way, preventive measures can be initiated when the risk is deemed to outweigh the side-effects. Overall, our study suggests that many major illnesses in association with immobilization increase the risk of venous thrombosis.

That the risk for venous thrombosis was higher in participants with a history of hemorrhagic stroke (odds ratio 4.9; 95% CI 2.4-9.9) than in participants with a history of ischemic stroke (odds ratio 1.4; 95% CI 0.9-2.3) deserves additional comment. This finding might represent the less frequent use of thromboprophylaxis in patients with hemorrhagic stroke. In most epidemiological studies, hemorrhagic and ischemic stroke are combined.[4,18] However, one other study also found an higher risk of venous thrombosis in patients with hemorrhagic stroke than in patients with ischemic stroke.[14]

We defined immobilization as being bedridden at home for at least 4 days, being hospitalized, or having surgery within three months prior to the index date. We found high odds ratios for venous thrombosis for immobilization in combination with liver disease (odds ratio 8.3; 95% CI 2.8-24.4), kidney disease (odds ratio 31.7; 95% CI 7.6-132.1), rheumatoid arthritis (odds ratio 11.7; 95% CI 5.8-23.6) and arterial thrombosis (odds ratio 11.6; 95% CI 7.1-19.2). ACCP guidelines currently do not consider thromboprophylaxis for immobilized patients with these conditions. If other studies confirm our new findings, intervention trials for weighing the benefits and risks of thromboprophylaxis are recommended for these high-risk groups with a major illness.

It is important to note that the baseline risk of venous thrombosis in absence of immobilization is low (less than 1.4 per 1000 persons per year).[7] Therefore odds ratios of 2.1 (for kidney disease in the absence of immobilization), 2.5 (for multiple sclerosis in the absence of immobilization), 1.7 (for heart failure in the absence of immobilization), 3.3 (for hemorrhagic stroke in the absence of immobilization), and 1.2 (for arterial thrombosis in the absence of immobilization) would probably result in an absolute risk of venous thrombosis of less than 4.6 (3.3 times 1.4) per 1000 persons per year in patients with these major illnesses. Thus, if

patients with any of these major illnesses were treated with long term thromboprophylaxis, the number needed to treat would be excessively high, while introducing a considerable risk of major bleeding. For this reason, thromboprophylaxis in patients with a major illness seems unjustified when no additional risk situations, such as hospitalization or surgery, are present.

An intriguing observation in our study was that myocardial infarction and angina were more clearly associated with pulmonary embolism than with deep vein thrombosis. Other studies also showed that the risk of pulmonary embolism was higher than for deep vein thrombosis in persons with such comorbidity.[4,18] This observation may be due to misclassification, which is possible as signs and symptoms of arterial thrombosis can be similar to pulmonary embolism. Alternatively, it may also be a causal observation as angina or myocardial infarction reflect local inflammatory effects in the lungs, which may lead to an increased risk of pulmonary embolism.[26]

The strengths of this study include the large patient sample, the detailed information about immobilization in both patients and controls, and the combination with data on thrombophilia. A limitation of this study is that major illnesses were assessed via self-report and the exact diagnoses of these major illnesses were not available. In addition, no specific questions were asked about the (severity of) major illnesses. However, since these are major diseases with a large impact, we expect that both patients and control persons reported their illnesses to a similar extent, thus limiting recall bias. Any resulting random misclassification would lead to an underestimation of our odds ratios. A second limitation of this study is that the blood sample was collected after the thrombotic event. Therefore, we cannot exclude the possibility that differences in plasma levels of the coagulation factors between cases and control persons were the result of the thrombotic event itself. However, the blood draw was performed at least 3 months after the thrombotic event, diminishing the possibility that the thrombotic event itself caused abnormalities in coagulation factor levels through acute phase reactions. A third limitation was that, as we had no data on the time between major illness and the subsequent venous thrombotic event in our study, we could not calculate specific risk estimates for different time frames. Not many previous studies were able to calculate a risk of venous thrombosis after major illness diagnosis, specified on time. However, the one that could showed that the risk was highest shortly after the major illness was diagnosed.[18] Therefore, our relative risk estimates would probably have been higher if we could have taken this time aspect into close consideration. A fourth limitation was that for participation as a case in MEGA, those who died soon after a first venous thrombotic event (4% of the patient population) were excluded.[20] This probably has led to an underestimation of our risk estimates, since patients with a major illness are more likely to die from venous thrombosis than patients without a major illness. A fifth limitation of our study was that we had limited power for several analyses. This low power of the study may have led to some unexpected findings, like a higher risk of venous

thrombosis among participants with angina than among participants with prior ischemic stroke. This finding should therefore be interpreted with caution. A sixth limitation is that we had no information about thromboprophylaxis during immobilization. This probably led to an underestimation of our risk estimates, as it is likely that patients with a major illness receive more thromboprophylaxis than other persons. Another aspect was that the risk of venous thrombosis could be especially increased for particular conditions causing liver disease, kidney disease, or heart failure. However, we did not have this information in our study. Future studies are needed on this topic. A final aspect of our study was that we had two separate control groups. However, by having a control group partly consisting of partners of patients, we probably have conservative estimates as partners will be more likely to resemble the cases than random controls. Therefore, we would expect higher odds ratios when comparing to RDD controls than to partners. Nevertheless, results pointed in the same direction and were roughly similar when both control groups were analyzed separately. Therefore, we do not think that our results are affected by the two different control groups.
In summary, we have reported a detailed epidemiological analysis on the risk of first venous thrombosis in patients with a major illness. All major illnesses reported here were associated with an increased risk of venous thrombosis ranging from an odds ratio of 1.5 for rheumatoid arthritis and arterial thrombosis to 4.9 for hemorrhagic stroke. These risks were most pronounced at time of immobilization and in the presence of thrombophilia. These results could be a guide for future thromboprophylaxis decisions.

ACKNOWLEDGEMENTS

The authors thank the directors of the Anticoagulation Clinics of Amersfoort (M. H. H. Kramer), Amsterdam (M. Remkes), Leiden (F. J. M. van der Meer), The Hague (E. van Meegen), Rotterdam (A. A. H. Kasbergen), and Utrecht (J. de Vries-Goldschmeding) who made the recruitment of patients possible. The interviewers (J. C. M. van den Berg, B. Berbee, S. van der Leden, M. Roosen, and E. C. Willems of Brilman) performed the blood draws. The authors also thank I. de Jonge, R. Roelofsen, M. Streevelaar, L. M. J. Timmers and J. J. Schreijer for their secretarial and administrative support and data management. The fellows I. D. Bezemer, J. W. Blom, A. van Hylckama Vlieg, E. R. Pomp and L. W. Tick took part in every step of the data collection. C. J. M. van Dijk, R. van Eck, J. van der Meijden, P. J. Noordijk and T. Visser performed the laboratory measurements. We express our gratitude to all persons who participated in the MEGA study. Dr Lijfering is a Postdoc of the Netherlands Heart Foundation (2011T012). This research was supported by the Netherlands Heart Foundation (NHS 98.113), the Dutch Cancer Foundation (RUL 99/1992) and the Netherlands Organization for Scientific Research (912-03-033 2003). The funding sources were involved in neither the collection, interpretation, and analysis of the data nor the decision for the writing and submission of this report for publication.

REFERENCES

1. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost*. 2007;5:692-699.
2. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133:381S-453S.
3. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, III. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med*. 2000;160:809-815.
4. Huerta C, Johansson S, Wallander MA, Garcia Rodriguez LA. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. *Arch Intern Med*. 2007;167:935-943.
5. Sogaard KK, Horvath-Puho E, Gronbaek H, Jepsen P, Vilstrup H, Sorensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. *Am J Gastroenterol*. 2009;104:96-101.
6. Mahmoodi BK, ten Kate MK, Waanders F, Veeger NJ, Brouwer JL, Vogt L, Navis G, van der Meer J. High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome: results from a large retrospective cohort study. *Circulation*. 2008;117:224-230.
7. Mahmoodi BK, Gansevoort RT, Veeger NJ, Matthews AG, Navis G, Hillege HL, van der Meer J. Microalbuminuria and risk of venous thromboembolism. *JAMA*. 2009;301:1790-1797.
8. Ocak G, Verduijn M, Vossen CY, Lijfering WM, Dekker FW, Rosendaal FR, Gansevoort RT, Mahmoodi BK. Chronic kidney disease stage 1-3 increases risk of venous thrombosis. *J Thromb Haemost*. 2010;8:2428-2435.
9. Wattanakit K, Cushman M, Stehman-Breen C, Heckbert SR, Folsom AR. Chronic kidney disease increases risk for venous thromboembolism. *J Am Soc Nephrol*. 2008;19:135-140.
10. Matta F, Singala R, Yaekoub AY, Najjar R, Stein PD. Risk of venous thromboembolism with rheumatoid arthritis. *Thromb Haemost*. 2009;101:134-138.
11. Arpaia G, Bavera PM, Caputo D, Mendozzi L, Cavarretta R, Agus GB, Milani M, Ippolito E, Cimminiello C. Risk of deep venous thrombosis (DVT) in bedridden or wheelchair-bound multiple sclerosis patients: a prospective study. *Thromb Res*. 2010;125:315-317.
12. Howell MD, Geraci JM, Knowlton AA. Congestive heart failure and outpatient risk of venous thromboembolism: a retrospective, case-control study. *J Clin Epidemiol*. 2001;54:810-816.
13. Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. *Arch Intern Med*. 2000;160:3415-3420.
14. Skaf E, Stein PD, Beemath A, Sanchez J, Bustamante MA, Olson RE. Venous thromboembolism in patients with ischemic and hemorrhagic stroke. *Am J Cardiol*. 2005;96:1731-1733.
15. Eliasson A, Bergqvist D, Bjorck M, Acosta S, Sternby NH, Ogren M. Incidence and risk of venous thromboembolism in patients with verified arterial thrombosis: a population study based on 23,796 consecutive autopsies. *J Thromb Haemost*. 2006;4:1897-1902.
16. Reich LM, Folsom AR, Key NS, Boland LL, Heckbert SR, Rosamond WD, Cushman M. Prospective study of subclinical atherosclerosis as a risk factor for venous thromboembolism. *J Thromb Haemost*. 2006;4:1909-1913.
17. van der Hagen PB, Folsom AR, Jenny NS, Heckbert SR, O'Meara ES, Reich LM, Rosendaal FR, Cushman M. Subclinical atherosclerosis and the risk of future venous thrombosis in the Cardiovascular Health Study. *J Thromb Haemost*. 2006;4:1903-1908.

18. Sorensen HT, Horvath-Puho E, Sogaard KK, Christensen S, Johnsen SP, Thomsen RW, Prandoni P, Baron JA. Arterial cardiovascular events, statins, low-dose aspirin and subsequent risk of venous thromboembolism: a population-based case-control study. *J Thromb Haemost*. 2009;7:521-528.
19. Veeger NJ, Piersma-Wichers M, Tijssen JG, Hillege HL, van der Meer J. Individual time within target range in patients treated with vitamin K antagonists: main determinant of quality of anticoagulation and predictor of clinical outcome. A retrospective study of 2300 consecutive patients with venous thromboembolism. *Br J Haematol*. 2005;128:513-519.
20. van Stralen KJ, Rosendaal FR, Doggen CJ. Minor injuries as a risk factor for venous thrombosis. *Arch Intern Med*. 2008;168:21-26.
21. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA*. 2005;293:715-722.
22. Kuipers S, Cannegieter SC, Doggen CJ, Rosendaal FR. Effect of elevated levels of coagulation factors on the risk of venous thrombosis in long-distance travelers. *Blood*. 2009;113:2064-2069.
23. Lijfering WM, Rosendaal FR, Cannegieter SC. Risk factors for venous thrombosis - current understanding from an epidemiological point of view. *Br J Haematol*. 2010;149:824-833.
24. de Graaf MA, Jager KJ, Zoccali C, Dekker FW. Matching, an appealing method to avoid confounding? *Nephron Clin Pract*. 2011;118:c315-c318.
25. Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet*. 1999;353:1167-1173.
26. Schultz MJ, Haitsma JJ, Zhang H, Slutsky AS. Pulmonary coagulopathy as a new target in therapeutic studies of acute lung injury or pneumonia--a review. *Crit Care Med*. 2006;34:871-877.