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ORIGINAL ARTICLE

Old and new risk factors for upper extremity deep venous thrombosis

J. W. BLOM,* C. J. M. DOGGEN,* S. OSANTO† and F. R. ROSENDAAL*‡

*Departments of *Clinical Epidemiology; and †Oncology, Leiden University Medical Center, Leiden, The Netherlands; and ‡Hemostasis and Thrombosis Research Center, Leiden University Medical Center, Leiden, The Netherlands*

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Summary. *Background:* Well known risk factors for upper extremity deep venous thrombosis are the presence of a central venous catheter (CVC) and malignancy, but other potential risk factors, such as surgery, injury and hormone replacement therapy (HRT), have not yet been explored. *Methods:* We performed a population-based case-control study including 179 consecutive patients, aged 18–70 years with upper extremity deep venous thrombosis and 2399 control subjects. Participants reported on acquired risk factors in a questionnaire and factor V Leiden and prothrombin 20210A mutation were ascertained. Information on CVC was obtained from discharge letters. *Results:* Forty-two patients (23%) and one control subject (0.04%) had a CVC (OR_{adj}: 1136, 95% CI: 153–8448, adjusted for age and sex). Cancer patients without a CVC had an eightfold increased risk of venous thrombosis of the arm (OR_{crude}: 7.7, 95% CI: 4.6–13.0). Other evident risk factors were prothrombotic mutations, surgery, immobilization of the arm (plaster cast), oral contraceptive use and family history, with odds ratios varying from 2.0 up to 13.1. The risk in the presence of injury and during puerperium was twofold or more increased, although not significantly. In contrast HRT, unusual exercise, travel and obesity did not increase the risk. Hormone users had an increased risk in the presence of prothrombotic mutations or surgery. Obese persons (BMI > 30 kg m^{-2}) undergoing surgery had a 23-fold increased risk of arm thrombosis compared with non-obese persons not undergoing surgery. *Conclusion:* A CVC is a very strong risk factor for arm thrombosis. Most risk factors for thrombosis in the leg are also risk factors for arm thrombosis.

Keywords: risk factors, upper extremity, venous thrombosis.

Correspondence: F. R. Rosendaal, Department of Clinical Epidemiology, C9-P, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands.
Tel.: +31 71 5264037; fax: +31 71 5266994; e-mail: f.r.rosendaal@lumc.nl

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Introduction

The annual incidence of venous thrombosis is 0.1% increasing with age to 1% [1]. Approximately 4% of all cases of venous thrombosis are located in the arm [2]. Complications associated with upper extremity venous thrombosis are pulmonary embolism (11–26%) [3], superior vena cava syndrome (21–23%) [4,5] and postthrombotic syndrome (27–50%) [3,6].

Known risk factors for deep venous thrombosis of the arm differ from risk factors of venous thrombosis of the leg or pulmonary embolism. Central venous catheters (CVCs) contribute to the risk of upper extremity venous thrombosis in 7–41% of all cases [7–10]. Other specific risk factors are effort-related compression of the deep veins of the upper extremity and compression caused by the thoracic outlet syndrome (Paget–Schroetter syndrome) [3]. Risk factors for venous thrombosis of the leg or pulmonary embolism, i.e. malignancy, use of oral contraceptives, pregnancy and thrombophilia have also been described as a risk factor for venous thrombosis of the arm [10–12]. However, most studies on arm thrombosis were of limited size and have not examined many of the other risk factors known to affect leg thrombosis, such as surgery, injury and hormone replacement therapy (HRT), as well as immobilization, travel, obesity and puerperium.

The occurrence of a venous thrombotic event often depends on the presence of more than one risk factor simultaneously and on the interaction between risk factors [13]. Most patients with a CVC also have cancer. CVCs are used to administer chemotherapy or other drugs. Irritation of the vessel wall by the chemotherapeutic agent in addition to the hypercoagulable state because of malignancy may add to the increased risk caused by the CVC. Likewise, additional presence of acquired and genetic risk factors, such as a CVC and the factor (F)V Leiden mutation, could increase the risk of thrombosis even more.

In the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis study (MEGA-study), a large population-based case–control study evaluating risk factors for venous thrombosis we included 179 unselected, consecutive patients with upper extremity deep venous thrombosis. We assessed the effect of acquired and genetic risk factors, which are highly prevalent. Additionally, we investigated the risk in the joint presence of FV Leiden, the

prothrombin 20210A mutation and malignancy and other known risk factors of venous thrombosis.

Methods

Patient inclusion

This study was performed within the MEGA study, an ongoing large population-based case–control study. The design of the MEGA study is described in detail elsewhere [14]. In the MEGA study consecutive patients aged 18–70 years, with a first deep venous thrombosis of the leg or arm or a first pulmonary embolism were included. Patients were identified at six anticoagulation clinics in the Netherlands. Anticoagulation clinics monitor the anticoagulant therapy of all patients in a well-defined geographical area, which allowed the identification of consecutive, unselected patients with venous thrombosis. From March 1999 until September 2003, 181 consecutive patients had a first deep venous thrombosis of the arm. One patient died of cancer soon after the venous thrombosis. All other 180 patients were invited to participate in our study. One patient refused to participate, thus 179 patients were included in the study leading to a response rate of 99.4%.

Discharge letters, collected from the general practitioner or from the hospital in which patients had been treated for venous thrombosis, were used to check for diagnostic methods. For 87% of the patients ($n = 156$) a discharge letter could be obtained. For 124 patients an objective diagnosis was documented. The diagnosis was objectively confirmed by ultrasound (119 patients), contrast venography (two patients) and computed tomography (three patients). For 32 patients we could not retrieve information on diagnostic methods from the discharge letter. These patients and those without a discharge letter ($n = 23$) were treated for at least 3 months with oral anticoagulants and were included in the analysis.

Of the 179 participating patients, 169 had venous thrombosis of the arm only, and nine cases (5%) also had a pulmonary embolism. The latter were objectively diagnosed using ventilation-perfusion scintigraphy. One patient had venous thrombosis of the arm in combination with venous thrombosis of the leg, confirmed by ultrasonography.

Control subjects were partners of patients with venous thrombosis, aged 18–70 years without a history of venous thrombosis, participating in the overall MEGA study from March 1999 until November 2002. Of all participating patients, 75% had a partner of whom 79% participated as control subject ($n = 2399$) [14].

Data collection

All participants were asked to fill in a questionnaire on acquired risk factors for venous thrombosis within a few weeks after the thrombotic event, and were subsequently seen for a blood draw 3 months after discontinuation of the anticoagulant therapy. When the participant was unable to fill in the questionnaire we asked questions by phone, using a standard mini-questionnaire (one patient and 62 control subjects). We used the date of diagnosis of thrombosis as the index date for patients. For control subjects the index date was the date of diagnosis of thrombosis of their partner (patient). Questions about acquired risk factors, such as surgery, immobilization by plaster cast, injury, unusual exercise (decorating, unusual heavy gardening, sawing, chopping wood was specifically asked for) and travel by car, bus, train or plane for more than 4 h were included in the analysis for a time window of 3 months prior to the index date. Injury was defined as rupturing or bruising of muscles or tendons, repetitive strain injury, tenosynovitis or bursitis. A history of malignancy, weight and height, use of oral contraceptives or HRT, pregnancy, puerperium (defined as a period of 3 months after delivery) at the index date, family history (defined as having one or both parents with a history of venous thrombosis before the age of 50) was also recorded in the questionnaire. We defined a diagnosis of malignancy 5 years or less before the index date as 'active cancer' [14]. Patients with absence of surgery in the previous 3 months, absence of CVC in the previous month, absence of active cancer, absence of puerperium, oral contraception, injury, plaster cast or prothrombotic mutation were defined as patients with idiopathic thrombosis of the arm.

Because we expected CVCs and cancer to be the most important risk factors, we took efforts to obtain more elaborate information on these items. Information about the presence or absence of a CVC in the month prior to the index date was obtained from the discharge letters of patients. To obtain this information from control subjects, we sent a short questionnaire to the general practitioner of those subjects who indicated a hospital admission or surgery within 3 months prior to the index date ($n = 61$). If a discharge letter or information from the general practitioner was unavailable or inconclusive we interviewed the participant by telephone (20 patients and nine control subjects). We received information for 98% of the patients and 97% of the control subjects. For participants without information we assumed absence of a CVC.

For individuals who indicated they had been diagnosed with cancer, additional information regarding origin of the cancer and stage of disease was gathered from their physician. Participants with non-invasive skin cancer were not considered as cancer patients (none of the patients and 21 control subjects). For the patient who died soon after the venous thrombosis as well as for patients and control subjects who refused to participate ($n = 1$ and 540, respectively), we verified the diagnosis of cancer by information available from the anticoagulation clinic or by phone [14].

All participants filled in an informed consent form and gave permission to obtain information about their medical history. This study was approved by the Ethics Committee of the Leiden University Medical Center.

Blood collection and laboratory analysis

Blood samples were taken 3 months after discontinuation of anticoagulant therapy. DNA was isolated to ascertain the FV

Leiden mutation (G1691A, gene ID:2153) or the prothrombin G20210A mutation (gene ID:5624). From persons who were unable to give a blood sample and from participants included from June 2002 onwards, we obtained a buccal swab, sent by mail, for DNA analysis.

Blood samples were drawn into vacuum tubes containing 0.1 volume 0.106 mol L^{-1} trisodium citrate as anticoagulant. The blood sample was separated into plasma and cells through centrifugation. Using a salting-out method, high molecular weight DNA was extracted. This was stored at −20 °C until amplification. DNA-analysis for the FV Leiden mutation and the prothrombin mutation was performed using a combined PCR method. Assessment of these mutations in DNA retrieved from the buccal swabs was performed identically to the method for DNA obtained from whole blood. A detailed description of this method is described previously [14]. DNA was available for 144 patients and 2018 control subjects. Potential risk factors measured in blood plasma such as high factor VIII levels, have not been investigated in the present study.

Statistical analyses

Odds ratios (OR) were calculated as an approximation of relative risks. The OR indicate the relative risk of venous thrombosis in the presence of a risk factor relative to the absence of that risk factor. A 95% confidence interval is given according to the method of Woolf [15]. Using a multiple logistic regression model, OR were adjusted for age and sex (OR_{adj}). In an extra analysis the risk of surgery, immobilization (plaster), injury and active cancer was adjusted for each of these factors by using a multivariable logistic regression model.

In the analysis of the effect of advanced stage of cancer, different types of cancer, and the joint presence of cancer and the FV Leiden mutation or the prothrombin 20210A mutation, cancer patients are those with 'active cancer'. Patients with cancer diagnosed longer than 5 years ago were excluded from these particular analyses.

To assess the effect of two risk factors simultaneously, OR were calculated in the presence of only one risk factor and in the presence of both risk factors, both relative to those with neither risk factor present. SPSS for Windows version 12.0.1 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

The 179 patients with deep venous thrombosis of the arm and 2399 control subjects had a median age of, respectively 45.1 (5th–95th percentile: 20.5–67.2) and 50.2 (5th–95th percentile: 28.4–66.4) years. There were 100 women (55.9%) in the patient group and 1202 women (50.1%) in the control group. In 56% of the patients the left arm was involved and in 44% the right arm. There were 17 patients with idiopathic thrombosis.

Central venous catheter

Patients with a CVC (42 of 179) had a highly increased risk to develop deep venous thrombosis of the arm (OR_{adj} 1136, 95% CI: 153–8448; Table 1). Thirty patients had a CVC for the administration of chemotherapy, nine for other reasons, such as parenteral feeding, bone-marrow transplantation, hemodynamic monitoring of shock and for three patients the indication of the catheter could not be ascertained. One control subject had a CVC for hemodynamic monitoring of a septic shock in the month before the index date.

Malignancy

For all cancer patients (including cancer diagnosed more than 5 years ago), taking also cancer among non-participants into account (one of two cases and one of 540 control subjects) and assuming a CVC was absent for non-participants, the crude odds ratio was 17.9 (OR_{crude} 17.9, 95% CI: 12.0–26.7) and 7.7 for cancer patients without a CVC (OR_{crude} 7.7, 95% CI: 4.6–13.0).

Table 1 Risk associated with central venous catheter (CVC) and active malignancy

	Patients (n = 179)	Control subjects (n = 2399)	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
CVC				
CVC absent	137	2398	1 (reference)	1 (reference)
CVC present	42	1	735 (100–5381)	1136 (153–8448)
Active malignancy†				
All participants, including CVC				
Malignancy absent	121	2322	1 (reference)	1 (reference)
Malignancy present	46	35	25.2 (15.7–40.6)	43.6 (25.5–74.6)
All participants, CVC excluded				
Malignancy absent	114	2321	1 (reference)	1 (reference)
Malignancy present	18	35	10.5 (5.8–19.1)	18.1 (9.4–35.1)

*Adjusted for age and sex.

†Patients with cancer longer than 5 years ago are excluded from this analyses (nine cases and 38 control subjects), as well as three cases and four control subjects of whom date of diagnosis was unknown.

Table 2 Acquired risk factors for upper extremity venous thrombosis within 3 months before index date, excluding users of a central venous catheter

Risk factor	Patients ($n = 137$)	Control subjects ($n = 2398$)	Odds ratio (95% CI)*	Adjusted odds ratio (95% CI)*†
Surgery upper extremity	2	3	11.8 (2.0–71.0)	13.1 (2.1–80.6)
Surgery elsewhere	10	38	5.0 (2.4–10.3)	4.7 (2.2–9.7)
Immobilization arm (plaster)	3	7	7.6 (2.0–29.9)	7.0 (1.7–29.5)
Injury upper extremity	4	30	2.4 (0.8–6.9)	2.1 (0.7–6.2)
Unusual exercise	23	303	1.3 (0.8–2.1)	1.5 (1.0–2.1)
Travel by car, bus, train, plane	18	257	1.2 (0.7–2.1)	1.3 (0.8–2.2)
body mass index				
< 25 kg m^{-2}	61	770	1 (reference)	1 (reference)
25–30 kg m^{-2}	56	1175	1.5 (0.9–2.7)	1.2 (0.7–2.2)
> 30 kg m^{-2}	17	328	0.9 (0.5–1.6)	0.9 (0.5–1.6)
Family history	17	107	3.0 (1.8–5.2)	2.8 (1.6–4.9)
Women 18–49 years	$n = 48$	$n = 534$		
Oral contraceptive use	28	176	2.8 (1.6–5.2)	2.0 (1.1–3.8)
Pregnancy	0	9	–	–
Puerperium	1	2	5.7 (0.5–63.6)	3.1 (0.3–35.5)
Women 40–69 years	$n = 44$	$n = 947$		
Hormone replacement therapy	5	90	1.2 (0.5–3.1)	1.2 (0.5–3.2)

Information of all risk factors available for more than 95% of patients and for more than 93% of control subjects.
*Reference group for each risk factor is the group without the risk factor.
†Adjusted for age and where applicable for sex.

Among the 167 patients, 46 (27.5%) had a history of active malignancy prior to the venous thrombosis, as compared with 35 (1.5%) of the 2357 control subjects (Table 1). The OR for active malignancy was 25.2 (OR_{crude} 25.2, 95% CI: 15.7–40.6). After adjustment for age and sex, the OR became 43.6 (OR_{adj} 43.6, 95% CI: 25.5–74.6). The adjusted OR of venous thrombosis for active malignancy in the absence of a CVC was 18.1 (OR_{adj} 18.1, 95% CI: 9.4–35.1; Table 1).

Of 46 patients with active cancer, 27 women and 19 men, including patients with a CVC, 16 had gastro-intestinal cancer (35%), 10 hematological cancer (22%) and four patients had lung cancer (9%). Seven of 27 women had breast cancer and three had ovarian cancer (26% and 11% of female patients with active cancer respectively). There were no women with cervix cancer, and no men with prostate cancer among the 19 men with cancer. Six patients had other types of cancer (13%). Of 35 control subjects with active cancer three had gastro-intestinal cancer (9%), two hematological cancer (6%) and one lung cancer (3%). Nine of 23 women had breast cancer (39%), two women ovarian cancer (9%) and one woman cervix cancer (4%). Six of 12 men had prostate cancer (50%). Eleven control subjects had other types of cancer (32%).

Among patients with active cancer without a CVC, the OR of venous thrombosis was 11.5 in the presence of distant metastases compared with active cancer patients without distant metastases (OR_{adj} 11.5, 95% CI: 1.6–80.2). The analysis was limited to those with solid tumors, i.e. 15 cases and 29 control subjects.

Acquired risk factors

The analysis of other acquired risk factors was restricted to individuals without a CVC, including 137 patients and 2398 control subjects. Cancer patients without a CVC were included in this analysis. Several risk factors, which play an important role in the risk of venous thrombosis of the leg, such as surgery and immobilization (plaster) also increased the risk for deep venous thrombosis of the arm (Table 2). Injury also increased the risk although not significantly. Additional analyses in which adjustment for each of these risk factors and for active cancer was made, led to similar OR. Only slightly more patients (16.9%) were performing unusual heavy exercise in the 3 months prior to the index date compared with control subjects (13.5%). Travel by car, bus, train or plane in the 3 months before the index date did not clearly affect the risk of upper extremity deep venous thrombosis. The adjusted OR for travel by plane alone was 0.9 (95% CI: 0.4–2.3; five cases and 98 control subjects). There was no increase in risk for individuals with a BMI > 25 kg m^{-2} compared with individuals with a BMI < 25 kg m^{-2}. The OR associated with a family history of venous thrombosis was 2.8 (OR_{adj} 2.8, 95% CI: 1.6–4.9). Oral contraceptive use and puerperium increased the risk of upper extremity venous thrombosis among women, whereas HRT did not increase the risk. Restriction of the above analyses to 124 objectively diagnosed cases gave similar results.

Prothrombotic mutations

Overall the allele frequency of FV Leiden among control subjects was 2.9%. There were 17 heterozygotes for the FV Leiden mutation out of 144 patients (11.8%) and 108 of 2018 control subjects (5.4%). No homozygotes for the FV Leiden mutation were found among patients and four (0.2%) among control subjects. Including the participants with CVC the risk of thrombosis in the presence of the FV Leiden mutation was

2.2-fold increased (OR_{adj} 2.2, 95% CI: 1.3–3.8). The allele frequency of the prothrombin G20210A mutation among control subjects was 1.0%. Seven patients (4.9%) had the heterozygous (20210 GA) variant compared with 42 control subjects (2.1%). No homozygotes for the prothrombin G20210A mutation were found. The risk of thrombosis in the presence of the prothrombin G20210A mutation was 2.3-fold increased (OR_{adj} 2.3, 95% CI: 1.0–5.2). Two control subjects were double heterozygotes.

Malignancy and prothrombotic mutations

We evaluated the joint effect of the FV Leiden mutation and the prothrombin 20210A mutation and active malignancy after exclusion of patients with a CVC (Table 3). The OR for carriers of a prothrombotic mutation without a malignancy was 2.7 (OR_{adj} 2.7, 95% CI: 1.6–4.7; Table 3). Individuals with only malignancy had an OR of 12.6 (OR_{adj} 12.6, 95% CI: 5.4–29.4) compared with non-carriers without malignancy. Carriers of a prothrombotic mutation who also had cancer had a OR of 177.1 (OR_{adj} 177.1, 95% CI: 17.4–1806.1). This implies that cancer patients with a prothrombotic mutation had a 20-fold increased risk of venous thrombosis compared with non-carriers with cancer (OR_{adj} 20.0, 95% CI: 1.5–273.7). When patients with a CVC were included, cancer patients with a prothrombotic mutation had a sixfold increased risk of venous thrombosis compared with non-carriers with cancer (OR_{adj} 6.0, 95% CI: 0.6–62.0).

Acquired risk factors and prothrombotic mutations

Oral contraceptive users without a prothrombotic mutation had an OR of 1.8 (OR_{adj} 1.8, 95% CI: 0.8–3.9). In the presence of a prothrombotic mutation we found an OR of 9.2 for oral contraceptive users compared with non-users without a mutation (OR_{adj} 9.2, 95% CI: 2.8–30.2; Table 4). Users of HRT without a prothrombotic mutation had an OR of 1.6 (OR_{adj} 1.6, 95% CI: 0.5–4.7), which increased to 5.4 in the presence of a prothrombotic mutation (OR_{adj} 5.4, 95% CI: 0.6–47.8; Table 4).

Table 3 Active malignancy, prothrombotic mutations, and the risk of arm thrombosis, excluding users of a central venous catheter

Factor V Leiden/ prothrombin 20210A	Active cancer	Patients $n = 109$	Control subjects $n = 1987$	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
No	No	78	1806	1 (reference)	1 (reference)
No	Yes	9	28	7.4 (3.4–16.3)	12.6 (5.4–29.4)
Yes	No	19	152	2.9 (1.7–4.9)	2.7 (1.6–4.7)
Yes	Yes	3	1	69.5 (7.1–675.4)	177.1 (17.4–1806.1)

DNA-samples were available for 109 of 137 patients without CVC and 1987 of 2398 control subjects without CVC.
*Adjusted for age and sex.

Table 4 Oral contraceptive (OC) use, hormone replacement therapy (HRT) at index date, body mass index (BMI: kg m^{-2}), prothrombotic mutations, and the risk of upper extremity venous thrombosis, excluding users of central venous catheter

		Factor V Leiden/ prothrombin 20210A	Patients	Control subjects	Odds ratio* (95% CI)	Adjusted OR (95% CI)†
OC‡	Yes	Yes	6	11	10.9 (3.5–33.8)	9.2 (2.8–30.2)
HRT§	Yes	Yes	1	5	4.4 (0.5–37.8)	5.4 (0.6–47.8)
Surgery¶	Yes	Yes	2	4	11.0 (2.0–60.6)	12.6 (2.2–73.5)
		Surgery				
OC**	Yes	Yes	3	3	19.9 (3.7–106.2)	13.7 (2.5–76.2)
HRT††	Yes	Yes	1	1	27.8 (1.7–454.9)	29.4 (1.8–490.3)
BMI (kg m^{-2})‡‡	< 25	Yes	3	19	2.1 (0.6–7.2)	2.0 (0.6–6.9)
	25–30	Yes	5	16	4.1 (1.4–11.5)	4.6 (1.6–13.5)
	> 30	Yes	4	3	17.4 (3.8–79.7)	23.0 (4.9–109.1)

Analysis for participants with DNA available (> 82% of cases and > 84% of control subjects) and who filled in the specific question in the questionnaire.
*Reference group for each risk factor is the group with neither risk factor present.
†Adjusted for age and where applicable for sex.
‡Women 18–49 years: 42 patients and 452 control subjects.
§Women 40–69 years: 34 patients and 793 control subjects.
¶All participants: information available 112 patients and 2003 control subjects.
**Women 18–49 years: 47 patients and 527 control subjects.
††Women 40–69 years: 41 patients and 909 control subjects.
‡‡All participants: information available for 133 patients and 2253 control subjects.

Patients without a prothrombotic mutation undergoing surgery had an increased risk of venous thrombosis of the arm (OR 3.5, 95% CI: 1.4–8.8). Carriers of a prothrombotic mutation, women using oral contraceptives and HRT or individuals with a BMI over 25 kg m^{-2} had a higher risk of upper extremity venous thrombosis when in a postoperative period of up to 3 months (Table 4). The OR for obese people undergoing surgery compared with non-obese people undergoing surgery is 7.1 (95% CI: 1.3–37.8).

Discussion

In this population-based case–control study the overall risk of upper extremity venous thrombosis was 18-fold increased in patients with cancer (including cancer diagnosed more than 5 years ago). Cancer patients without a CVC had an eightfold increased risk whereas a CVC increased the risk of arm thrombosis 1100-fold. Patients with active cancer and a prothrombotic mutation had a 20-fold increased risk compared with patients with active cancer and without a prothrombotic mutation. Several risk factors for deep vein thrombosis of the lower extremity, such as prothrombotic mutations, surgery, immobilization of the arm (plaster cast), oral contraceptive use and family history, also affected the risk of arm thrombosis. The risk in the presence of injury and during puerperium increased, but not significantly. However, some risk factors, such as HRT, obesity and travel did not increase the risk of arm thrombosis. For several risk factors this risk was enhanced in the presence of prothrombotic mutations or when undergoing surgery.

Central venous catheter and malignancy

Twenty-three percent of the thrombosis patients had a CVC, which is therefore by far the most important prevalent risk factor for upper extremity thrombosis; this confirms two studies also including consecutive, unselected patients describing a incidence of 30% [10,16].

The risk of upper extremity venous thrombosis in cancer patients is increased mainly but not exclusively because of CVCs. Whereas 61% of the patients with a malignancy had a CVC, cancer patients without a CVC had an eightfold increased risk of venous thrombosis of the arm, similar to the risk of venous thrombosis of the leg or pulmonary embolism [14]. A previous case-control study found a 2.6-fold increased risk for cancer patients [10]. In the latter patients with arm complaints but not objectively diagnosed venous thrombosis participated as control subjects. This may explain the difference as more control subjects suffered from cancer (9.7% vs. 1.5% active cancer in the MEGA-study).

Compared with cancer patients with venous thrombosis of the leg or pulmonary embolism, we found relatively more arm thrombosis patients with hematological cancer and cancer of the esophagus or stomach [14]. These patients received chemotherapy by CVC [data not shown]. Additionally, patients with esophagus or stomach cancer usually receive parenteral nutrition by CVC after surgery thereby increasing the risk of venous thrombosis. The distribution of types of cancer in patients without a CVC is similar as shown before in patients with deep venous thrombosis or pulmonary embolism [14].

Cancer patients with distant metastases had a 12-fold increased risk of venous thrombosis compared with cancer patients without distant metastases. In the analysis of distant metastases, type of cancer and the combined presence of cancer and prothrombotic mutations we defined active cancer as cancer diagnosed within 5 years before the index date. This might cause slight misclassification because we did not verify the activity of the malignancy in the medical records. Cancer in remission could have been more often classified as active cancer, which could have led to underestimation of risks.

Acquired risk factors

Risk factors that play a role in deep venous thrombosis of the leg or pulmonary embolism such as surgery, immobilization (plaster cast) and oral contraceptive use also increased the risk of upper extremity venous thrombosis in the MEGA-study. HRT did not clearly increase the risk. Earlier reports were inconclusive on hormone use [8,10,17], probably because of small sample size and inclusion of referred selected patients.

A frequently described risk factor of upper extremity venous thrombosis is unusual exercise, especially in individuals with well developed thoracic musculature or anomalies leading to a narrow thoracic outlet. We found a slight increase in risk of upper extremity venous thrombosis for individuals performing unusual exercise, in accordance with another case–control study [10]. Although much attention is usually paid to the thoracic outlet syndrome [2], only for one patient in our study this syndrome was spontaneously reported in the discharge letter.

It has been suggested in a case-series of five patients that air travel can contribute to the development of upper extremity venous thrombosis [18]. We did not find an increase in risk for travel by car, bus, train or plane, neither was there an increase in risk for travel by plane alone.

Malignancy and prothrombotic mutations

Patients with cancer and a prothrombotic mutation had a highly increased risk of venous thrombosis compared with non-carriers without cancer. A recent study of breast cancer patients with CVCs found a sixfold increased risk of venous thrombosis for carriers of the FV Leiden mutation compared with non-carriers, similar to our results for overall cancer [19].

Other acquired risk factors and prothrombotic mutations

Odds ratios of venous thrombosis for the FV Leiden mutation and the prothrombin 20210A mutation were slightly higher in an Italian case-control study, which is likely to be due to a selected patient group in the latter [8]. We found a synergistic effect between oral contraceptive use or HRT and

prothrombotic mutations. Both these findings were analogous to those described earlier in patients with upper and lower extremity venous thrombosis or a pulmonary embolism [20–22]. High risks were seen for surgical patients particularly when they used exogenous hormones or were obese.

Although our study is one of the largest studies of patients with deep venous thrombosis of the arm, a limitation of the study is the small number of cases. This small number is a reflection of the low incidence of deep venous thrombosis of the arm. As a consequence the confidence intervals of several of our analyses are wide, indicating unstable estimates of the OR. However, as this is one of the few studies comparing patients with arm thrombosis to the general population and one of the first studies evaluating interaction between risk factors in patients with arm thrombosis, this may give indications for further study.

Clinical implications

As the incidence of arm thrombosis is only 4% of the total incidence of venous thrombosis, the absolute risk remains very small for all risk factors except CVCs. Screening for genetic risk factors in the general population in order to avoid arm thrombosis by subsequent prophylactic treatment is therefore not an issue. Although risks are increased in surgical patients, patients using oral contraception or HRT and cancer patients, screening for prothrombotic mutations does not seem to be useful in these patient groups either.

Assuming an incidence of venous thrombosis of one per 1000 per year, in patients with a CVC we would expect a yearly absolute incidence of: 1136 (OR) $\times$ 1/1000 (incidence venous thrombosis overall) $\times$ 1/25 (4%) = one per 22 patients with a CVC. These figures are in line with a recent publication in which we followed patients with CVC's [23]. In this study we found a cumulative incidence of clinically manifest thrombosis of 7.1% after 1 year of follow up. A recent review study describes cumulative incidences from 0% to 12% [24]. For patients with FV Leiden or the prothrombin 20210A mutation the risk is 2.7-fold increased compared with patients with a CVC but without these mutations [23]. Prophylactic anticoagulation in patients with a CVC is not yet a standard procedure. Three studies have shown a beneficial effect of anticoagulant prophylaxis in cancer patients with CVCs [25–27]. More recent studies failed to show a beneficial effect thus far in cancer patients [28–30]. However, complete data of the latter studies have to be awaited. A review on CVC related thrombosis concluded that routine prophylaxis for patients with a CVC is still debatable [24]. In view of the high risk of arm thrombosis for patients with a CVC future trials should explore which patients with a CVC could benefit from anticoagulant prophylaxis.

Conclusion

Generally, risk factors for venous thrombosis of the arm are the same as those for venous thrombosis of the leg, apart from HRT, obesity and travel. A specific risk factor for arm thrombosis is a the presence of a CVC.

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