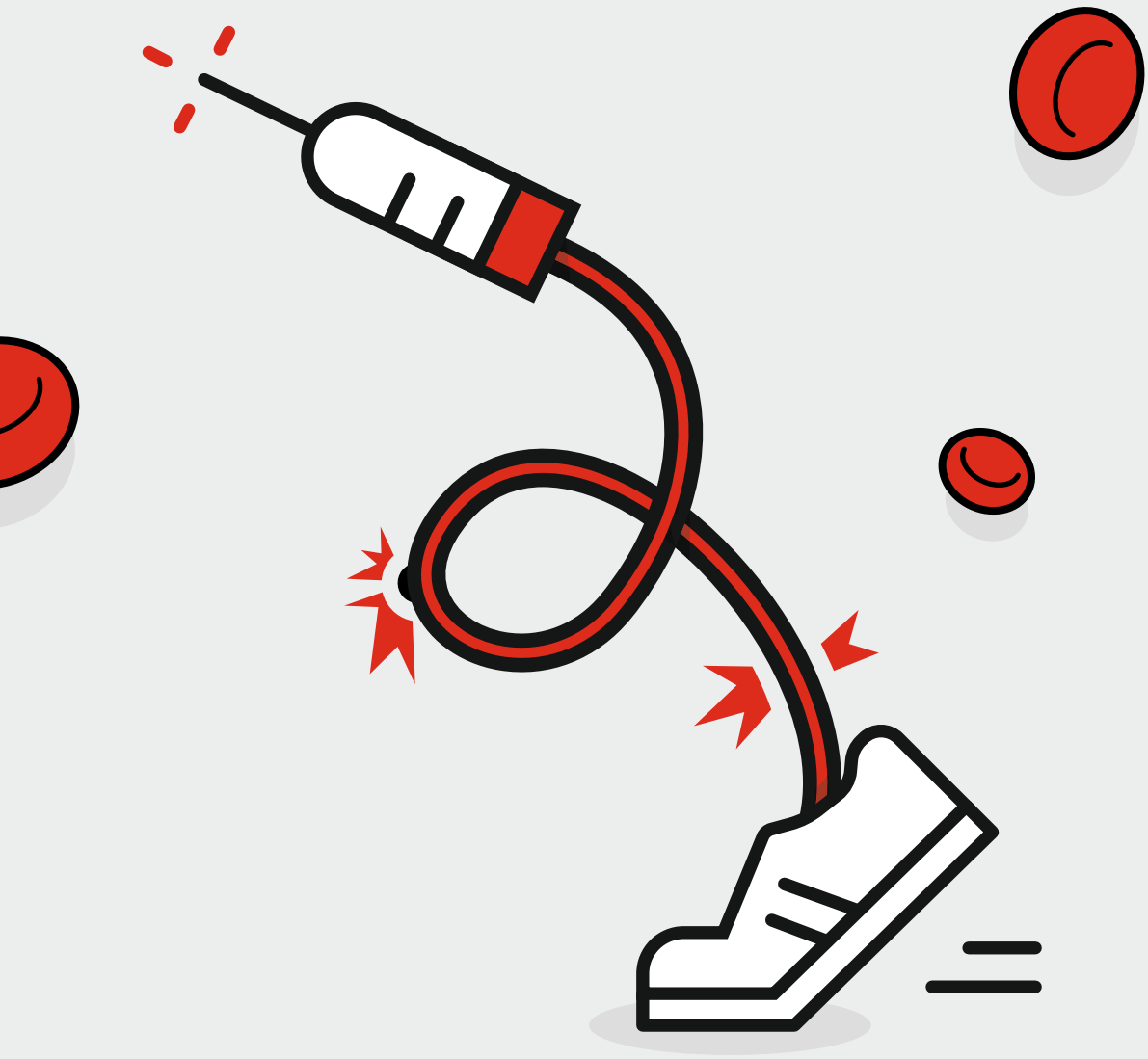
Thrombosis prophylaxis after knee arthroscopy or **during lower leg cast immobilization**

Determining the balance between benefits and risks.



Raymond Alexander van Adrichem

Thrombosis prophylaxis after knee arthroscopy or during lower leg cast immobilization

Determining the balance between benefits and risks

Proefschrift
Door

Raymond Alexander van Adrichem

The work described in this thesis was performed at the Department of Clinical Epidemiology and the Department of Orthopedic Surgery of the Leiden University Medical Center, the Netherlands
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Proefschrift

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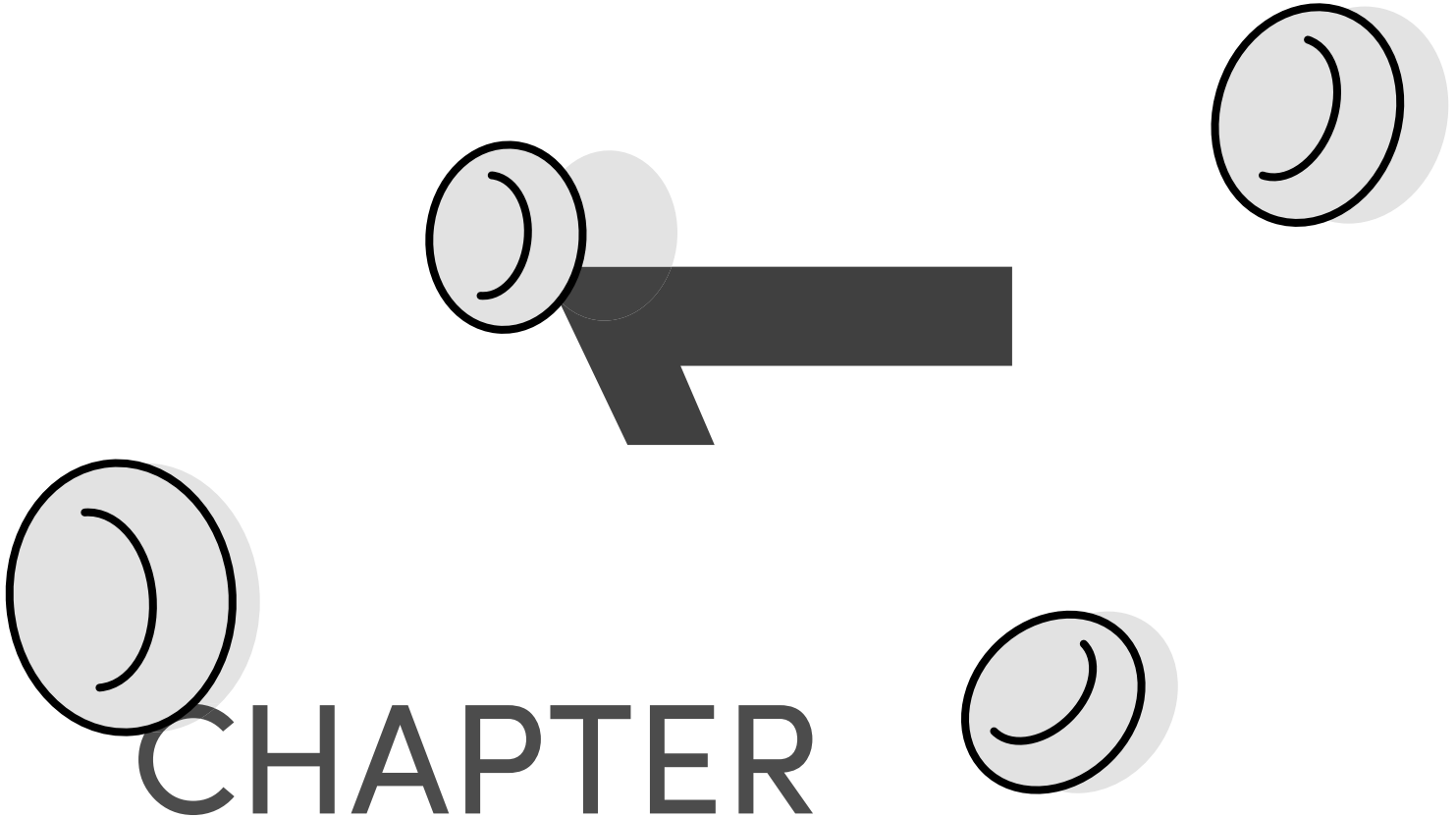
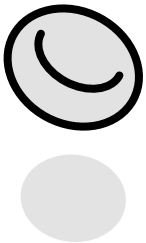
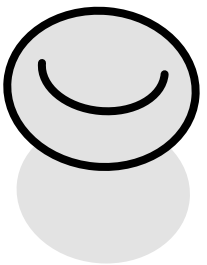
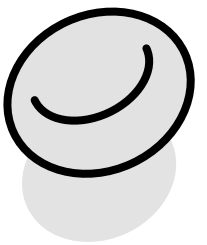


CHAPTER

General introduction and outline of this thesis







Venous thromboembolism (VTE), i.e. deep vein thrombosis (DVT) or pulmonary embolism (PE), is the third most common cardiovascular disease and occurs in 1-2 per 1000 person years in the general population.[1-5] Of all patients with VTE, around two thirds are diagnosed with DVT and one third with PE.[1] The mortality rate of VTE is high, being about 12% in non-cancer patients in one year.[1] Furthermore it leads to chronic morbidity. For example, within two years, up to 50% of patients with DVT develop post-thrombotic syndrome and 4% of patients with a PE suffer from pulmonary hypertension.[6,7]

In the last decades, many risk factors for VTE have been identified, both genetic and environmental.[8-10] An important risk factor is orthopaedic surgery with an estimated risk of 4% in the 35 days after major orthopedic surgery. Therefore, thrombosis prophylaxis is recommended for most orthopedic procedures.[11,12]

The magnitude of the VTE risk is however not well established for all orthopedic surgery patients. In patients with lower leg cast immobilization the risk of asymptomatic VTE varies from 4-40% during the immobilization period.[13-18] However, the relevance of asymptomatic VTE is unclear since these VTEs usually disappear without symptoms.[19] In contrast to this, the cumulative incidence of symptomatic VTE is far less, varying between 0-5.5%. Furthermore, this risk is inflated by the inclusion of patients with complete leg cast immobilization, without further stratification within these studies.[13-18]

The same methodological problem arises when evaluating the VTE risk in patients after arthroscopy of the knee, which is one the most common orthopedic procedures world-wide, being performed over 4 million times each year.[20] Also in these patients the extend of the risk of VTE is not known. Rates of asymptomatic thrombosis in the control groups of six randomized trials that assessed thrombosis prophylaxis to placebo in patients who had an arthroscopy of the knee varied between 0 and 16%.[21-26] This wide variation in incidence can be explained by differences in follow-up time, varying from one week to 3 months. In addition, patients with more extensive procedures, such as anterior cruciate ligament reconstructions, were also included in four out of six trials, further inflating the risk. Rates of symptomatic thrombotic events, however, were once again much lower and varied between 0 and 5.3%.[21-26] The risk of symptomatic VTE after arthroscopic ACL reconstruction is estimated to be higher (4% in 8 weeks compared to regular knee arthroscopy)[27] because of its more invasive nature (e.g. harvesting autologous

tendon graft, tibial and femoral drilling). Once again, no further distinction between types of arthroscopic procedures was made in the afore mentioned trials. Only one trial exclusively focused on the effect of thromboprophylaxis after ACL reconstruction but included only 36 patients.[28] This trial is therefore largely underpowered and no conclusions can be drawn from this study.

Because of the use of asymptomatic VTE as the primary outcome in trials addressing thromboprophylaxis in patients with lower leg cast immobilization and arthroscopic knee surgery, while presence of symptomatic VTE is of more clinical significance, and as a consequence the limited number of included patients in these trials, an overall risk-benefit balance on thromboprophylaxis cannot be established. Therefore, national and international guidelines are unable to give clear recommendations regarding prophylactic treatment in these patients.[11,12,29] For that matter, large pragmatic clinical trials using symptomatic VTE as primary endpoint are needed to address this problem in these highly frequent interventions (i.e. lower leg casting and arthroscopy).[11]

Aim of this thesis

Since the magnitude of the risk of VTE during cast immobilization of the lower extremity and after arthroscopic knee surgery is unknown, this risk will be studied using a large population-based case-control study, the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA study[30]). In addition, the combined effect on VTE risk of these treatments with well-known genetic and acquired risk factors for VTE will be established (chapter 2 and 3).

Since guidelines cannot give clear recommendations based on current evidence, the clinical practice regarding VTE prophylaxis in these patients in the Netherlands will be studied with a survey study among trauma and orthopedic surgeons. In addition, the rationale for providing prophylactic treatment to these patients is studied (chapter 4).

To provide evidence for the effect of pharmacological VTE prophylaxis in patients during lower leg cast immobilization and after knee arthroscopy, two large pragmatic randomized clinical trials are performed using symptomatic VTE as the primary outcome. In chapter 5 the effect of low-molecular weight heparin on the prevention of symptomatic VTE during cast immobilization of the lower leg will be described (POT-

CAST trial). In chapter 6 the results of low-molecular weight heparin on the prevention of symptomatic VTE after knee arthroscopy will be given (POT-KAST trial).

Because the VTE risk is estimated to be higher after ACL reconstruction, modes of VTE prevention in these patients will be studied separately. In chapter 7 the effect of pharmacological prophylaxis compared to compression stockings after arthroscopically assisted ACL reconstruction will be given.

Lastly, to be able to study individualized VTE prophylaxis treatment strategies, prediction models using the predictive value of genetic, environmental, coagulation factors and other biomarkers for the development of VTE during cast immobilization of the lower extremity and after knee arthroscopy will be developed and validated. The results of these prediction models will be given in chapter 8 and 9.

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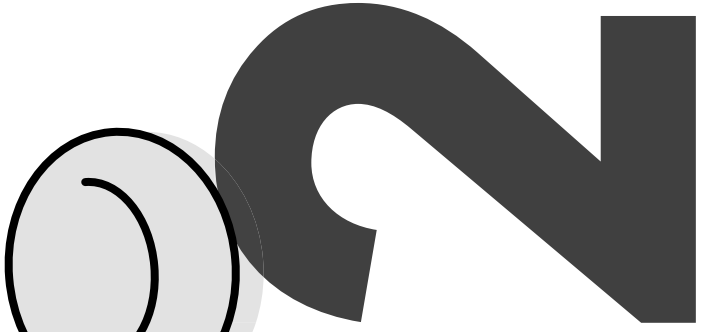
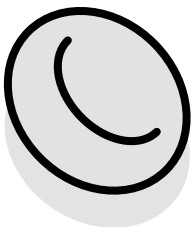


CHAPTER

Below-knee cast immobilization and risk of venous thrombosis: results from a large population-based case-control study



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J Thromb Haemost 2014; 12: 1461-9

Abstract

Background

From the available evidence the risk of venous thrombosis in patients with below-knee cast immobilization remains unclear. The objective of this study was to estimate the risk of venous thrombosis after below-knee cast immobilization and to identify high risk groups.

Patients and Methods

We used data from a large population-based case-control study (MEGA-study) into the etiology of venous thrombosis (4418 cases, 6149 controls). Odds ratios (OR) with 95% confidence intervals (CI95) were calculated and adjusted for age, sex, BMI and regular exercise. Absolute risks were estimated from the ORs.

Results

134 patients and 23 controls had below-knee plaster cast in the year before the index-date, resulting in an 8-fold increased risk (OR 8.3 (CI95; 5.3-12.9)). Traumatic indications led to a higher risk than non-traumatic indications: OR 12.7 (CI95; 6.6-24.6) vs OR 7.6 (CI95; 0.9-66.4). An additionally increased risk was found for combinations with genetic or acquired risk factors: oral contraceptives OR 18.2 (CI95; 6.2-53.4); obesity OR 17.2 (CI95; 5.4-55.2); Factor V Leiden, Factor II 20210A mutation and/or non-O blood type OR 23.0 (CI95; 11.5-46.0), all for the period of one year. In the first three months after cast application 90% of the events occurred. This led to a 56-fold increased risk (OR 56.3 (CI95; 17.9-177.3)) in this period.

Conclusions

Below-knee cast immobilization strongly increases the risk of venous thrombosis. We found distinct differences in intrinsic risk per person with respect to indication of cast immobilization and presence of genetic or acquired risk factors.

Introduction

The incidence rate of a first venous thrombosis, i.e. deep vein thrombosis and pulmonary embolism, in the general population is 1 - 2 per 1000 person years.[1-5] Venous thrombosis is a serious condition leading to chronic morbidity, including post-thrombotic syndrome and pulmonary hypertension, and increased mortality. Post-thrombotic syndrome is seen in 23% to 60% of patients within two years after a symptomatic deep vein thrombosis[6] and about 4% of patients with a pulmonary embolism develop chronic pulmonary hypertension within two years.[7] The mortality rate of venous thrombosis is high and estimated at 1.8% in the first month in non-cancer patients with a deep vein thrombosis and 6.8% in non-cancer patients with a pulmonary embolism.[1]

Many risk factors for venous thrombosis have been identified, both genetic and environmental.[8,9] One of these known risk factors is cast immobilization, especially immobilization of the lower extremity[10,11]. However, the exact size of the risk due to lower leg cast immobilization is not known. Cumulative incidences in the control groups of six randomized controlled trials comparing thromboprophylaxis to placebo (numbers of patients: 53-223) in patients with lower extremity cast immobilization ranged from 4% to 40% during the immobilization period.[12-17] The majority of these events, however, were asymptomatic. These venous thromboses usually disappear without symptoms and it is unclear what proportion progresses to clinical disease. The cumulative incidences of symptomatic venous thrombosis in the control groups were much lower and ranged from 0 to 5.5% (reported in three trials).[13,15,17] Also, these trials not only included patients with below-knee cast immobilization, but also with cylindrical and complete leg cast immobilization. Because these patients have more extensive trauma, the risk of venous thrombosis in patients with below-knee plaster cast may have been overestimated. In two cohort studies only in patients with below-knee cast immobilization who did not receive thromboprophylaxis, somewhat lower symptomatic venous thrombosis risks were found: 0.6% in three months in 1174 patients and 1.8% in one year in 381 outpatients.[18,19]

Partly because the exact risk of venous thrombosis in patients with below-knee cast immobilization remains unclear, international guidelines on thromboprophylaxis are reluctant to advise in favor of routine anticoagulant treatment. Also, as information on high risk groups is limited, characteristics that increase the risk are generally not taken into account in these guidelines.[20-22]

The aims of the present study were to estimate the risk of symptomatic venous thrombosis after cast immobilization, particularly below-knee cast immobilization, to identify the indications for below-knee plaster cast that contribute most to this risk (e.g. type of injury or type of treatment) and to analyze the combined effect of cast immobilization with well-known genetic and acquired risk factors for venous thrombosis. We studied this in a large population-based case-control study, the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study.[23,24]

Methods

Study population

Between March 1, 1999 and August 31, 2004 all consecutive patients between the age of 18-70 years with a first deep vein thrombosis or pulmonary embolism were identified at six anticoagulation clinics (originating from a well-defined geographical area) in the Netherlands. Patients with severe psychiatric problems or unable to speak Dutch were considered ineligible. Patients with a primary deep vein thrombosis of the upper extremities were excluded in the current analysis. Of the 6237 patients eligible, 276 died before they were able to fill in the questionnaire and 82 were at the end stage of a disease, leaving 5876 patients of whom 4956 participated (84%) (See flowchart, figure1). The diagnosis deep vein thrombosis or pulmonary embolism was confirmed by information of the diagnostic procedure, obtained via hospital records and family physicians and included (Doppler) ultrasonography, ventilation-perfusion scan, angiography and spiral CT-scan.

The control-group included two groups, i.e. 3297 partners of participating patients (88% participation rate) and 3000 controls, identified using a random digit dialing method (69% participation rate) .[25,26] The random controls were frequency matched with respect to sex and age.

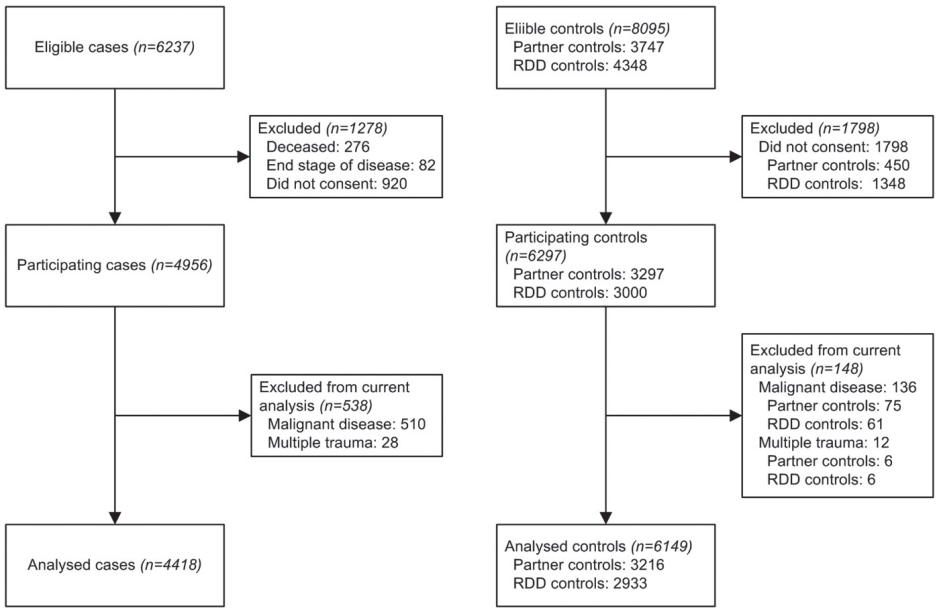

Figure 1. *Flow chart of eligible and analyzed cases and controls.*
Description: Flow chart of eligible and analyzed cases and controls. RDD: Random digit dialing controls.

Data collection

All participants completed a questionnaire on risk factors for venous thrombosis. In addition to general questions on demographics and specific questions on potential risk factors for thrombosis, the questionnaire included questions about trauma or injury covering the period of one year before the index date and about cast immobilization, such as indication for immobilization. The index date was defined as date of diagnosis of the thrombotic event for patients and partner controls and as the date of completing the questionnaire for random digit dialing controls.

DNA collection and laboratory analysis

DNA was collected by means of a blood sample from patients and control subjects included from the start of the study until May 31, 2002. In patients and controls included after June 1, 2002 and in those unable to visit the clinic for a blood sample, DNA was collected by means of buccal swabs sent by mail. DNA was analyzed on F5, rs6025 (Factor V Leiden) and F2, rs1799963 (prothrombin 20210A) mutations. Both mutations

were measured simultaneously by a multiplex polymerase chain reaction using the TaqMan assay.[27] ABO-blood group was also analyzed using the TaqMan assay.[28] Laboratory technicians were blinded to whether the samples came from patients or controls.

Statistical analysis

Estimates of relative risks were determined by calculation of odds ratios (OR) with their 95% confidence intervals (95CI). Using binary logistic regression, odds ratios were at all times adjusted for sex and age (ORadj) to take the frequency matching into account, and additionally, for the putative confounders body mass index (BMI, weight in kilograms divided by height in meters squared) and regular exercise. Regular exercise was classified as physically active sport activities of at least once a week. Obesity was defined as a BMI above 30 kg/m2, according to the WHO classification of overweight and obesity.[29] Missing values for the confounders BMI and regular exercise were imputed by multiple imputation[30] (missing values for BMI were present in 9.0% of cases and 8.1% of controls, missing values for regular exercise in 11.2% of cases and 8.9% of controls. There were no missing values for sex and age). Patients with known malignancies or a history of malignant disease as well as multiple trauma patients were excluded from the analysis as the baseline risk and the mechanism of thrombosis are different in these patients. For reasons of statistical precision, time windows of one year before the event were mostly used. When possible a time window of three months was used. Traumatic reasons for cast immobilization included fractures, tendon and ligament ruptures, ankle distortions and contusions; non-traumatic indications included overuse injuries, plantar fasciitis and non-descriptive joint complaints. In addition, the risk of venous thrombosis was calculated separately for deep vein thrombosis and pulmonary embolism. For this, patients with both deep vein thrombosis and pulmonary embolism were categorized as having a pulmonary embolism. Furthermore, the venous thrombosis risk was calculated per age-category (10-year age strata).

To analyze a possible joint effect between plaster cast and Factor V Leiden, prothrombin G20210A or blood group non-O, odds ratios and adjusted odds ratios were calculated for cast immobilization in the presence of one genetic risk factor in relation to none of the genetic risk factors. Possible joint effects were also analyzed for the combination of cast immobilization with obesity, the combination with oral contraception use (in women below 50 years of age) and the combination with one or more of the above mentioned

genetic or acquired risk factors. For all statistical analyses SPSS version 20.0.0 (IBM, Armonk, New York, US) was used.

Ethics statement

All participants gave written informed consent and the study was approved by the Medical Ethics Committee of the Leiden University Medical Centre.

Results

A total of 4418 cases and 6149 controls were included for this analysis (figure 1). Their demographics are shown in table 1. Of the cases, 134 (3%) had below-knee cast immobilization one year prior to the index date and so had 23 (0.4%) controls. This corresponds with an over eightfold increased risk of venous thrombosis in the following year after below-knee cast immobilization. (table 2). Of these 134 patients, 95 (70.1%) had a deep vein thrombosis and 39 (29.1%) a pulmonary embolism, corresponding to a 10-fold increased and a 6-fold increased risk, respectively (ORadj 10.2; 95CI 6.4 – 16.2 for DVT and ORadj 5.8; 3.4 – 9.8 for PE). Most thromboses (90%) were seen in the first three months after cast application (figure 2a), leading to a 56-fold increased risk (OR 56.3; CI95; 17.9-177.3) in this period (120 patients and 3 controls had a below-knee cast 3 months before the index date). Odds ratios were higher in conservatively treated patients than in surgically treated patients (table 2). Trauma related indications for a below-knee cast in non-surgically treated patients (OR 12.7; CI95; 6.6-24.6) were more strongly associated with venous thrombosis risk than non-traumatic indications (OR 7.6; CI95; 0.9-66.4), as shown in table 2.

Table 1. *Characteristics of study population*

	Patients	**Control Subjects**
	n=4418	**n=6149**
Sex, Women, *n (%)*	2420 (54.8)	3297 (53.6)
Median Age, *y (5th-95th percentile)*	48.5 (25.3 - 67.5)	47.5 (25.3 - 66.5)
Median BMI*, *kg/m^2 (5th-95th percentile)*	26.4 (20.2 - 35.5)	25.0 (19.8 - 33.1)
Regular exercise, *n (%)*	1453 (32.9)	2391 (38.9)
Type of venous Thrombosis		
DVT†, *n (%)*	2580 (58.4)	NA
PE‡, *n (%)*	1431 (32.4)	NA
DVT+PE, *n (%)*	407 (9.2)	NA

Table 1. *Characteristics of study population (continued)*

	Patients n=4418	**Control Subjects n=6149**
Cast immobilization§, *n*	227	76
Lower extremity, *n*	203	36
Complete leg, *n*	53	7
Knee (foot and ankle free), *n*	4	1
Below-knee, *n*	134	23
Foot (ankle free), *n*	12	5
Upper extremity, *n*	21	39
Complete arm, *n*	5	8
Upper arm brace (elbow free), *n*	0	1
Forearm (incl wrist), *n*	16	28
Hand (wrist free), *n*	0	2
Corset (immobilization of the spine), *n*	3	1

** BMI: body mass index in kg/m²*

† DVT: deep vein thrombosis

‡ PE: pulmonary embolism

§ Cast immobilization within one year before the index date

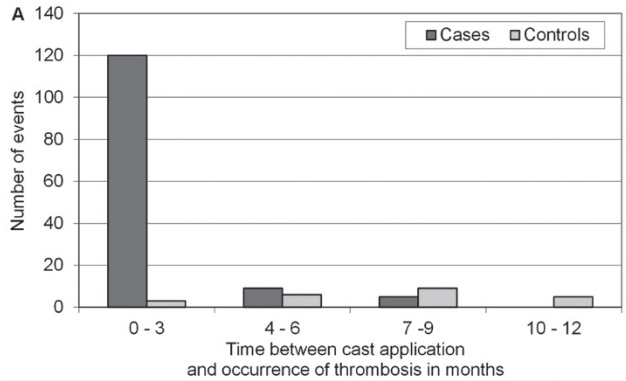

Figure 2a. *Frequency of the occurrence of events in months within one year after below-knee cast application.*

Description: Time between cast application and occurrence of venous thrombosis is defined as difference between date of cast application and diagnosis of venous thrombosis in the cases or the index date in the controls.

Table 2. *Treatment type and indication of below-knee cast immobilization and the risk of venous thrombosis within one year.*

Treatment	Patients*	Control Subjects	OR_{adj}† (95CI‡)	OR_{adj}§ (95CI)
None	4191	6073	1 (Reference)	1 (Reference)
Below-knee cast	134	23	8.5 (5.4 - 13.2)	8.3 (5.3 - 12.9)
Operative	41	11	5.4 (2.7 - 10.4)	4.9 (2.5 - 9.6)
Conservative	93	12	11.4 (6.2 - 20.7)	11.4 (6.2 - 20.9)
Traumatic	86	10	12.6 (6.5 - 24.3)	12.7 (6.6 - 24.6)
Non-Traumatic	5	1	7.6 (0.9 - 65.5)	7.6 (0.9 - 66.4)

** Of two patients no information on indication of cast immobilization was available.*

† OR_{adj}: adjusted odds ratio, adjustment for sex and age

‡ 95CI: 95% confidence interval

§ OR_{adj}: adjusted odds ratio, adjustment for sex, age, BMI and regular exercise.

Cast immobilization in general was associated with a fourfold increased risk of venous thrombosis in one year (227 (5.1%) patients, 23 (0.4%) controls (OR 4.3 (95CI 3.3 – 5.6)). Results for different types of upper extremity, spine and lower extremity cast immobilization are shown in the supplemental table.

Time between below-knee cast application to the development of venous thrombosis and duration of immobilization.

Time between date of cast application and development of venous thrombosis for the first 3 months is shown in figure 2b for the below-knee cast patients. Almost two thirds of the patients were diagnosed with venous thrombosis in the first month after immobilization (62.5%), almost a quarter in the second month (24.2%) and still 13.3% in the third month. No clear relation could be observed for duration of below-knee cast immobilization with risk of venous thrombosis (Figure 2c).

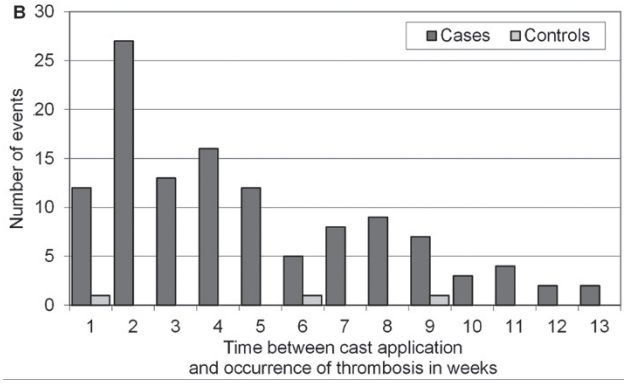

Figure 2b. *Frequency of the occurrence of events within the first 13 weeks after below-knee cast application.*

Description: Time between cast application and occurrence of venous thrombosis is defined as difference between date of cast application and diagnosis of venous thrombosis in the cases or the index date in the controls.

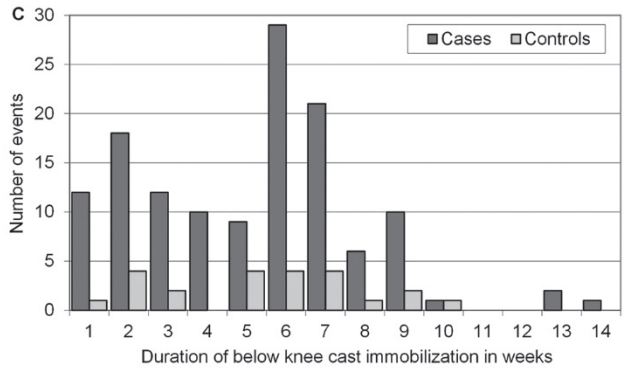

Figure 2c. *Frequency of the occurrence of events for different durations of below-knee cast immobilization.*

Description: The duration of immobilization is defined as the time between diagnosis of venous thrombosis in the cases or the index date in the controls and cast removal. For three cases no information on duration of below knee cast immobilization was available.

Acquired and genetic risk factors and below-knee cast immobilization

In table 3 relative risks for the combination of acquired and genetic risk factors and a below-knee cast are shown. 1558 of the female patients and 1867 of the female controls were below 50 years of age. Of these, information was available on hormonal contraception use in 1525 patients and 1841 controls. The combination of oral contraception use with below-knee cast immobilization was associated with an 18-fold increased risk of venous thrombosis (ORadj 18.2; 95CI 6.2 – 53.4) in the year after cast immobilization compared with women without a cast and who did not use oral contraception. Of the 29 women who used oral contraceptives, had below knee cast immobilization and developed venous thrombosis, three (10.3%) were carrier of the Factor V Leiden mutation, two (6.9%) were carrier of the prothrombin G20210A mutation and one (3.4%) was carrier of both mutations.

A 17 times higher risk for obese patients with below-knee cast immobilization was found than for non-obese patients without cast immobilization (ORadj 17.2; 95CI 5.4 – 55.2).

Of 3838 (86.9%) patients and 4710(76.6%) controls, information on genetic risk factors was available. Carriers of the Factor V Leiden mutation, prothrombin G20210A mutation or a non-O blood type who also had below-knee cast immobilization had a 23 times higher risk of venous thrombosis in the following year than non- carriers and patients with blood type O without cast immobilization (ORadj 23.0; 95CI 11.5 – 46.0). In addition, we found that the risk of venous thrombosis increased strongly with increasing number of acquired or genetic risk factors present in combination with below-knee cast immobilization (table 3). We did not find any clear differences in thrombosis risk for the different age groups (table 4). Analysis for the risk of venous thrombosis per age group for men and women separately showed similar results (data not shown).

Table 3. *Joint effects of below-knee cast immobilization and oral contraception use in women below 50 years of age, obesity (BMI>30kg/m2, factor V Leiden, prothrombin 20210 A mutation or non-O blood type and the risk of venous thrombosis within one year*

Acquired or genetic risk factor	Below knee cast Immobilization	Patients	Control subjects	OR_{adj}* (95CI†)	OR_{adj}‡ (95CI)
Oral contraception					
Absent	Absent	457	1139	1 (reference)	1 (reference)
Present	Absent	1029	695	3.8 (3.2 - 4.4)	3.9 (3.3 - 4.5)
Absent	Present	10	3	8.1 (2.2 - 29.7)	8.4 (2.3 - 31.4)
Present	Present	29	4	18.3 (6.4 - 52.5)	18.2 (6.2 - 53.4)
Obesity§					
Absent	Absent	3304	5269	1 (reference)	1 (reference)
Present	Absent	887	804	1.7 (1.6 - 1.9)	1.7 (1.5 - 1.9)
Absent	Present	98	20	8.0 (4.9 - 13.0)	8.3 (5.1 - 13.6)
Present	Present	36	3	17.4 (5.4 - 56.0)	17.2 (5.4 - 55.2)
Factor V Leiden					
Absent	Absent	3110	4445	1 (reference)	1 (reference)
Present	Absent	614	245	3.6 (3.1 - 4.2)	3.6 (3.1 - 4.2)
Absent	Present	97	17	8.1 (4.8 - 13.6)	8.1 (4.8 - 13.6)
Present	Present	17	2	12.5 (2.9 - 54.2)	11.0 (2.5 - 48.0)
Prothrombin G20210 A mutation					
Absent	Absent	3542	4597	1 (reference)	1 (reference)
Present	Absent	183	94	2.5 (2.0 - 3.2)	2.5 (2.0 - 3.2)
Absent	Present	108	19	7.4 (4.5 - 12.1)	7.2 (4.4 - 11.7)
Present	Present	6	0	∞	∞
Non-O Blood type					
Absent	Absent	1043	2152	1 (reference)	1 (reference)
Present	Absent	2664	2535	2.2 (2.0 - 2.4)	2.2 (2.0 - 2.4)
Absent	Present	32	11	6.0 (3.0 - 12.0)	5.7 (2.8 - 11.4)
Present	Present	82	8	21.2 (10.2 - 43.9)	20.9 (10.0 - 43.5)
Factor V Leiden and / or Prothrombin 20210A mutation and / or non-O blood type					
Absent	Absent	845	1994	1 (reference)	1 (reference)
Present	Absent	2864	2685	2.5 (2.3 - 2.8)	2.5 (2.3 - 2.8)
Absent	Present	25	10	5.9 (2.8 - 12.4)	5.6 (2.7 - 11.9)
Present	Present	89	9	23.4 (11.7 - 46.6)	23.0 (11.5 - 46.0)

Table 3. *Joint effects of below-knee cast immobilization and oral contraception use in women below 50 years of age, obesity (BMI>30kg/m2, factor V Leiden, prothrombin 20210 A mutation or non-O blood type and the risk of venous thrombosis within one year (continued)*

Acquired or genetic risk factor	Below knee cast Immobilization	Patients	Control subjects	OR_{adj}* (95CI†)	OR_{adj}‡ (95CI)
Number of risk factors present¶					
0	Absent	796	2527	1 (reference)	1 (reference)
0	Present	25	9	9.3 (4.2 - 20.2)	9.6 (4.4 - 21.1)
1	Present	57	11	18.3 (9.3 - 36.0)	18.1 (9.1 - 35.9)
2	Present	39	3	43.4 (13.4 - 141.0)	35.8 (10.9 - 117.5)
≥3	Present	13	0	∞	∞

* OR_{adj}*: adjusted odds ratio, adjustment for sex and age*

† *95CI: 95% confidence interval*

‡ OR_{adj}*: adjusted odds ratio, adjustment for sex, age, BMI and regular exercise.*

§*BMI: Body mass index in kg/m*^{2}

¶ *Presence of any the risk factors oral contraception, obesity, Factor V Leiden, Prothrombin G20210A mutation and Non-O blood type*

Table 4. *Below-knee cast immobilization and the risk of venous thrombosis within one year for different age categories.*

	Below-knee cast		No Cast			
Age	Patients	Control Subjects	Patients	Control Subjects*	OR_{adj}† (95CI‡)	OR_{adj}§ (95CI)
18 – 29	11	2	472	691	9.2 (2.0 - 43.2)	9.4 (2.0 - 44.3)
30 – 39	25	4	776	1233	10.3 (3.6 - 29.9)	10.3 (3.5 - 30.5)
40 – 49	40	9	1000	1479	6.8 (3.3 - 14.3)	6.0 (2.9 - 12.7)
50 – 59	40	6	1025	1619	10.9 (4.6 - 25.8)	11.1 (4.6 - 26.3)
60 – 69	18	2	918	1049	11.9 (2.7 - 51.7)	12.2 (2.8 - 52.7)

* *Two control subjects were above 70 years of age.*

† OR_{adj}*: adjusted odds ratio, adjustment for sex*

‡ *95CI: 95% confidence interval*

§ OR_{adj}*: adjusted odds ratio, adjustment for sex, BMI and regular exercise.*

Discussion

Cast immobilization is associated with an increased risk of symptomatic venous thrombosis. In this population-based case-control study, we found that all forms of cast immobilization combined led to a fourfold increase of venous thrombosis in the following year. An 8- fold increased risk of venous thrombosis was found in patients with below-knee cast immobilization. The risk was particularly high (56-fold increased) in the first three months, during which 90% of the cases occurred. Patients with a traumatic indication had a higher risk of venous thrombosis than patients with non-traumatic reasons for cast immobilization. We found a further increased risk for patients with a below-knee cast who had additional genetic or acquired risk factors (e.g. obesity, oral contraception, Factor V Leiden mutation and prothrombin G20210A mutation), with relative risks ranging between 17 and 23 compared with patients without a cast and such risk factors (all over one year following cast application. Lastly, we found that accumulation of several risk factors was present in patients who developed a thrombotic event.

A few studies previously reported on risk factors of venous thrombosis in patients with a below-knee cast. The severity of injury, age, obesity, presence of varicose veins, non-weight bearing cast immobilization and type of cast immobilization (rigid cast versus non-rigid cast) were found to be associated with a higher risk of venous thrombosis in previous studies.[13,14,31] None of these studies reported on the association between genetic and acquired risk factors, duration of immobilization or indication for below-knee cast immobilization and venous thrombosis, estimates that we could all provide in an unselected population.

Patients with immobilization of the knee, with foot and ankle free, had a lower risk estimate in our study compared with patients with below-knee cast immobilization (ankle immobilized). This result supports the theory that immobilization of the ankle and therefore the non-functioning of the skeletal muscle pump is key in the pathogenesis of venous thrombosis in patients with a below-knee cast. Nevertheless, the presence of trauma also seems to play an important role as can be inferred from the increased risk of VT in patients with a traumatic reason for cast immobilization in comparison with non-traumatic indications. In trauma patients, damage to vessel walls leads to the exposure of blood to collagen and tissue factor, thereby inducing the activation of the coagulation cascade. [32] The thus induced hypercoagulable state may explain the

higher risk of venous thrombosis in these patients than in those who are immobilized without tissue injury. We found a higher relative risk for deep vein thrombosis than for pulmonary embolism with a RR(PE)/RR (DVT)<1. This indicates that below-knee cast immobilization is a risk factor with a stronger effect on the occurrence of deep vein thrombosis than on pulmonary embolism.[33] This can possibly be explained as well by local coagulation activation and clot formation due to trauma and the non-functioning of the skeletal muscle pump due to immobilization.

We found a clear relation between time of immobilization and the development of venous thrombosis. Twice as many patients were diagnosed with venous thrombosis in the second week of immobilization as in the first week. This finding corresponds with the natural course of the disease, since a venous clot generally takes some time to develop and is in line with observations in patients with minor injuries and in patients who had surgery, in whom venous thrombosis rates were also higher in the second to fourth week.[34,35] Another explanation for the higher venous thrombosis rate in the second week can be that symptoms of deep vein thrombosis of the leg correspond with those of traumatic injuries and that it may take time for a patient and clinician to recognize these symptoms as deep vein thrombosis.

Several limitations need to be taken into account when interpreting our results. In our study we found a higher risk of venous thrombosis for conservatively treated patients with below-knee cast immobilization than surgically treated patients. To explain this finding, we can only speculate that patients who underwent surgery were more often treated with some form of thromboprophylaxis as their risk for venous thrombosis could have been perceived to be higher. However, a beneficial effect of thrombosis prophylaxis on (a)symptomatic venous thrombosis in such patients has not been demonstrated.[15,16,36] Unfortunately, no information was available on thromboprophylaxis use during cast immobilization. A Dutch survey performed in 2004 (the same period as our inclusion period) indicated that 30% of trauma surgery departments prescribed thromboprophylaxis (low molecular weight heparin) during below-knee cast immobilization and 79% prescribed prophylactic therapy in patients treated with a complete leg cast.[37] The absence of information on thromboprophylaxis use while a proportion of the patients most likely did receive some, implies that our risk estimate probably represents an underestimation of the true relative risk. Another potential limitation concerns the numbers in the subgroup analyses that were sometimes

small, for which reason we were not able to calculate three-month risk estimates for all subgroups and for which reason the confidence intervals in some of the subgroups were rather wide. Nevertheless, the point estimates and the lower limits of these confidence intervals were consistently high, indicating a high risk of VT in these subgroups. Thirdly, as the primary goal of our study was to estimate the risk of venous thrombosis in the lower extremity after below-knee cast immobilization, we did not include patients with upper extremity thrombosis in our study. However, an increased risk for upper extremity deep vein thrombosis in patients with cast immobilization of the arm has previously been described.[38] Furthermore, recall bias can play a role in case control studies. However, we believe cast immobilization of the lower extremity is a medical condition with a high impact independent of being a case or a control subject. Therefore, it is highly unlikely that recall of cast immobilization would differ between cases and controls. Lastly, due to the case-control design of our study, we could only estimate odds ratios as estimates of incidence rate ratios but no incidence rates. However, to give an indication of the absolute risk of venous thrombosis after below-knee cast immobilization, a 56-fold increased risk in three months corresponds to an estimated absolute risk of venous thrombosis of 1% over three months. (Based on an incidence of 0.75 per 1000 person-years in the general population in the age group included in our study (18-69 years)).[1]

Our findings in patients with additional genetic or acquired risk factors indicate that the risk of thrombosis differs strongly per individual as the presence of more risk factors leads to a higher risk of venous thrombosis. Identification of high-risk patients will help individualize prophylactic strategies in which situation patients with low thrombosis risk will not have to be needlessly exposed to the risks and burden of treatment with anticoagulants. Knowledge is needed on the effect of other risk factors for venous thrombosis in patients with a below-knee cast, such as malignancy and family history of venous thrombosis. From this information, prediction models can be developed of which the impact in clinical practice needs to be established in a randomized validation trial.[39,40]

In conclusion, patients with below-knee cast immobilization have a much increased risk of venous thrombosis, i.e. a 56-fold increased risk compared to patients with no cast, corresponding to an estimated incidence of 1% in the first three months after cast application. We found distinct differences in intrinsic risk of venous thrombosis per person. Taking factors such as indication of cast immobilization, as well as the presence

of genetic and acquired risk factors into account may lead to identification of high-risk patients. Further studies should be aimed at demonstrating the benefits of individualized thromboprophylactic treatment.

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Supplemental table

Location of all forms of cast immobilization and risk of venous thrombosis within one year and three months after cast application

Location	Patients	Control Subjects	OR_{adj}* (95CI†)	OR_{adj}‡ (95CI)
None	4191	6073	1 (Reference)	1 (Reference)
One year				
All	227	76	4.3 (3.3 - 5.6)	4.2 (3.2 - 5.5)
Upper Extremity	21	39	0.8 (0.4 - 1.3)	0.8 (0.5 - 1.3)
Spine	3	1	4.4 (0.5 - 42.4)	4.0 (0.4 - 39.0)
Lower Extremity	203	36	8.2 (5.7 - 11.7)	7.9 (5.5 - 11.4)
Complete leg	53	7	11.1 (5.0 - 24.4)	11.1 (5.1 - 24.8)
Knee (foot and ankle free)	4	1	5.8 (0.6 - 52.1)	5.1 (0.6 - 45.6)
Below-knee	134	23	8.5 (5.4 - 13.2)	8.3 (5.3 - 12.9)
Foot (ankle free)	12	5	3.5 (1.2 - 9.8)	2.8 (1.0 - 8.0)
Three months				
All	191	20	13.8 (8.7 - 21.9)	13.7 (8.5 - 21.7)
Upper Extremity	12	12	1.4 (0.6 - 3.2)	1.6 (0.7 - 3.7)
Spine	3	0	∞	∞
Lower Extremity	176	8	31.9 (15.7 - 64.9)	30.9 (15.2 - 63.0)
Complete leg	43	3	20.9 (6.5 - 67.6)	20.9 (6.5 - 67.6)
Knee (foot and ankle free)	3	1	4.3 (0.4 - 41.6)	3.6 (0.4 - 34.5)
Below knee	120	3	58.0 (18.4 - 182.4)	56.3 (17.9 - 177.3)
Foot (ankle free)	10	1	14.1 (1.8 - 110.2)	12.6 (1.6 - 98.9)

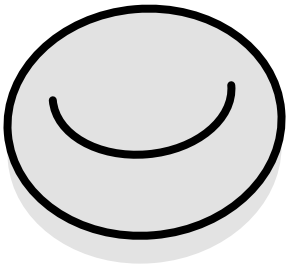
* OR_{adj}: *adjusted odds ratio, adjustment for sex and age*

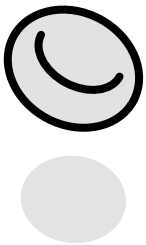
† *95CI: 95% confidence interval*

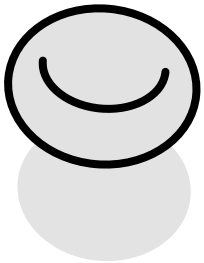
‡ OR_{adj}: *adjusted odds ratio, adjustment for sex, age, BMI and regular exercise.*

CHAPTER

Risk of venous thrombosis after arthroscopy of the knee: results from a large population-based case-control study







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J Thromb Haemost 2015; 13: 1441-8

Abstract

Background

From the currently available evidence the risk of venous thrombosis after knee arthroscopy remains unclear. Objective of this study was to estimate the risk of venous thrombosis after arthroscopy of the knee and to identify high risk groups.

Patients and methods

We used data from a large population-based case-control study (MEGA-study) into the etiology of venous thrombosis (4416 cases, 6150 controls). Odds ratios (OR) with 95% confidence intervals (CI95), adjusted for age, sex, body mass index, rheumatic disease and regular exercise were calculated.

Results

103 patients and 24 controls had a knee arthroscopy in the year before the index-date, resulting in a 6-fold increased risk (OR 5.9 (CI95; 3.7-9.3)). Ligament reconstructions led to a higher risk (OR 17.2 (CI95; 2.2-136)) than meniscal surgery, diagnostic arthroscopy or chondroplasty (OR 5.4 (CI95; 3.4-8.7)). An additionally increased risk was found for combinations with genetic and acquired risk factors: with oral contraceptives: OR 46.6 (CI95; 6.1-353); with Factor V Leiden, Factor II G20210A mutation or non-O blood type: OR 15.3 (CI95; 8.1-28.5). The risk of venous thrombosis was particularly high in the first three months after knee arthroscopy with an 18-fold increased risk (OR 16.2; 95CI 7.8 – 33.7)).

Conclusions

We observed a strongly increased risk of venous thrombosis after knee arthroscopy, especially in the first months after the procedure. The risk was particularly high in the presence of other acquired or genetic risk factors, making knee arthroscopy a high-risk intervention in certain individuals.

Introduction

Venous thrombosis (VT, the composite of deep vein thrombosis (DVT) and pulmonary embolism PE) affects 1 – 2 per 1000 persons per year in the general population and is a serious condition associated with increased morbidity and mortality.[1-7] One of the major risk factors for VT is orthopedic surgery.[8-10] While guidelines commonly recommend thrombosis prophylaxis for most orthopedic procedures, they advise against this for patients undergoing knee arthroscopy or arthroscopy-assisted knee surgery.[9,11,12] Although knee arthroscopy is the most commonly performed orthopedic procedure world-wide,[13] the magnitude of the risk of VT after knee arthroscopy is not well known, and the benefits of treatment can therefore not be weighed against the risks.[9,11] Furthermore, it is not well known how genetic and acquired risk factors or the indication for arthroscopy (e.g. meniscal tear, ligament reconstruction) influence the risk of thrombosis. Therefore, the aim of the present study was to estimate the risk of VT after knee arthroscopy and to assess the influence of genetic or additional acquired risk factors. We studied this in a large population-based case-control study, the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis study (MEGA- study).

Methods

Study population

Between March 1, 1999 and August 31, 2004 all consecutive patients between 18 – 70 years of age with an objectively diagnosed first DVT of the lower extremities or PE were identified at six anticoagulation clinics (serving a well-defined geographical area) in the Netherlands. Of the eligible patients, 4956 participated in the study (84% participation rate).[14]

In total 6237 control subjects were included in the study: 3297 partners of participating patients (88% participation rate) and 3000 controls identified using a random digit dialing method (69% participation rate).[15,16] The random digit dial controls were frequency matched with respect to sex and age.

Data collection

Participants completed a questionnaire on risk factors for VT, including orthopedic surgery, date and type of surgery, side and location (i.e. knee or ankle) and indication for surgery. A blood sample for DNA isolation was collected from the start of the study until June, 2002. After June 1, 2002 and for participants unable to visit the clinic, buccal swabs were sent by mail for DNA isolation. DNA was analyzed for Factor V Leiden (F5, rs6025) and prothrombin G20210A mutation (F2, rs1799963).[17] For ABO-blood group we determined the polymorphisms rs8176719, rs7853989, rs8176749 and rs8176750.[18] Laboratory technicians were blinded as to whether the samples came from patients or controls.

Statistical analysis

For the analysis, the index date was defined as date of diagnosis of the thrombotic event for patients and partner controls and as the date of completing the questionnaire for random digit dialing controls. Estimates of the relative risk were determined by calculation of odds ratios (OR) with their 95% confidence intervals (95CI). Odds ratios were at all times adjusted for sex and age (ORadj) to take the frequency matching into account, and additionally, for the confounders body mass index (BMI, weight in kilograms divided by height in meters squared), presence of rheumatic disease, regular exercise (classified as a frequency of physically active sport activities of at least once a week) and for a leg injury in the three months preceding the venous thrombotic event. Missing values for the confounders BMI (396 (9.0%) cases; 500 (8.1%) controls),

rheumatic disease (551 (12.5%) cases; 506 (8.2%) controls) and regular exercise (495 (11.2%) cases; 549 (8.9%) controls) were imputed by multiple imputation.[19] There were no missing values for sex and age. Patients with known malignancies or a history of malignant disease (510 cases; 136 controls) as well as patients with other surgical interventions (28 cases; 11 control), other forms of orthopedic surgery (243 cases; 106 controls) or additional cast immobilization of the lower extremity (2 cases; 0 controls) 3 months before or after knee arthroscopy and one case with Klinefelter syndrome were excluded from the analysis as the baseline risk and the mechanism of thrombosis are different in these patients (see figure 1 for flow chart). For maximum statistical precision, time frames of twelve months before the index date were mostly used to determine exposure to knee arthroscopy. When possible, a time window of three months was used. Indications for knee arthroscopy included meniscectomy, chondroplasty, diagnostic knee arthroscopy and ligament reconstructions. The VT risk was calculated for knee arthroscopy in general and for regular knee arthroscopy (meniscectomy, chondroplasty and diagnostic knee arthroscopy) and ligament reconstruction separately. In addition, separate analyses were performed for DVT and PE as outcome (patients with both DVT and PE were categorized as having a PE). Furthermore, the VT risk was calculated per 10 year age strata and for possible joint effects with factor V Leiden, prothrombin G20210A, blood group non-O, obesity (defined as a BMI equal to or above 30 kg/m2, according to the WHO classification of overweight and obesity[20]) and with oral contraception use in women below 50 years of age. Possible joint effects were also analyzed for the combination of knee arthroscopy with more than one of the above mentioned genetic or acquired risk factors. For all statistical analyses SPSS version 20.0.0 (IBM, Armonk, New York, US) was used.

Ethics statement

All participants gave written informed consent and the study was approved by the Medical Ethics Committee of the Leiden University Medical Centre.

Results

In total, 4416 venous thrombosis patients and 6150 controls were included in the analysis (see figure 1 for flow chart). 2423 (54.9%) patients and 3302 (53.7%) controls were women and 2585 (58.5%) of the patients had a deep vein thrombosis of the leg. Further demographics of the study population are shown in table 1.

Knee arthroscopy had been performed in 103 patients and 24 control subjects in the year previous to the index date, resulting in an almost 6-fold increased risk of VT (ORadj 5.9; 95CI 3.7 – 9.3) (table 2). Of these patients, 83 (81%) had a DVT of the leg and 20 (19%) a PE, corresponding to an 8- and 2.5-fold increased risk respectively (ORadj 8.0; 95CI 5.0 – 12.9 and ORadj 2.5; 95CI 1.4 – 4.6).

As can be seen in figure 2, the risk of VT was highest in the first weeks after arthroscopy and remained increased up to three months after the procedure. In this three-month period arthroscopy was associated with an over 16 times increased risk (ORadj 16.2; 95CI 7.8 – 33.7) of VT.

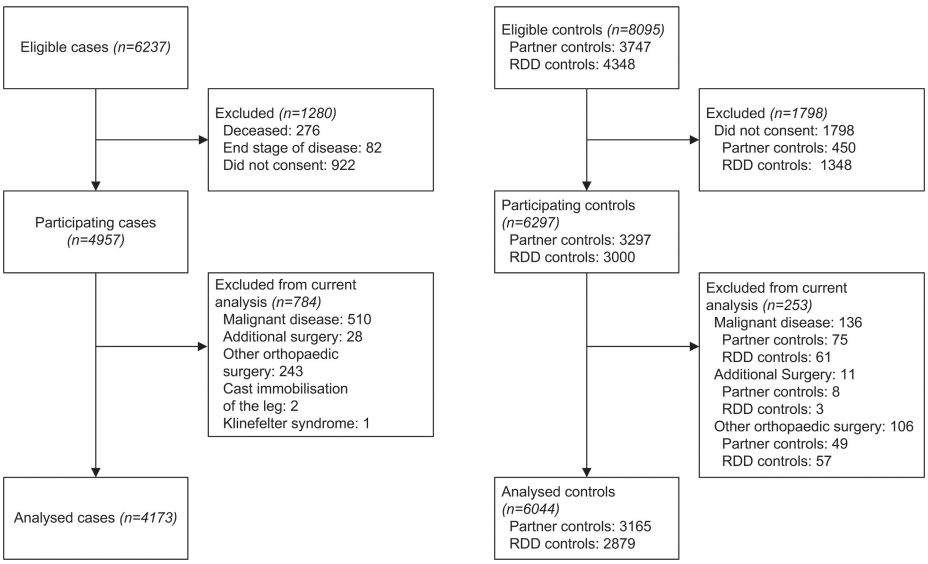

Figure 1. *Flow chart of eligible and analyzed cases and controls.*
Description: Flow chart of eligible and analyzed cases and controls. RDD: Random digit dialing controls.

Table 1. *Characteristics of study population*

	Patients	**Control subjects**
	n=4416	**n=6150**
Sex, women (%)	2423 (54.9)	3302 (53.7)
Age, median (5th - 95th percentile)	48.5 (25.3 - 67.5)	47.5 (25.3 - 66.5)
BMI*, median (5th - 95th percentile)	26.4 (20.2 - 35.5)	25.0 (19.8 - 33.1)
Regular sports activities (%)	1441 (32.6)	2390 (38.9)
Rheumatic disease (%)	228 (5.2)	155 (2.5)
Leg injury (%)	545 (12.3)	186 (3.0)
Type of venous thrombosis		
DVT† (%)	2585 (58.5)	NA
PE‡ (%)	1427 (32.3)	NA
DVT+PE (%)	404 (9.1)	NA
Orthopedic surgery (%)§	346 (7.8)	130 (2.1)
Knee arthroscopy	103	24
Regular ¶	91	23
Ligament reconstruction	12	1

* *BMI: body mass index in kg/m^2*

† *DVT: deep vein thrombosis*

‡ *PE: pulmonary embolism*

§ *Orthopedic surgery within one year before the index date*

¶ *Meniscectomy, chondroplasty and diagnostic knee arthroscopy*

Table 2. *Knee arthroscopy and the risk of venous thrombosis within one year*

Knee arthroscopy	**Patients (n=4173)**	**Control Subjects (n=6044)**	**ORadj* (95CI†)**	**ORadj‡ (95CI†)**
No orthopedic surgery	4070	6020	1 (Reference)	1 (Reference)
Knee arthroscopy	103	24	6.5 (4.2 - 10.2)	5.9 (3.7 - 9.3)
Regular§	91	23	6.0 (3.8 - 9.5)	5.4 (3.4 - 8.7)
Ligament reconstruction	12	1	18.9 (2.5 - 145.8)	17.2 (2.2 - 136.2)

* OR_{adj}*: adjusted odds ratio, adjustment for sex and age*

† *95CI: 95% confidence interval*

‡ OR_{adj}*: adjusted odds ratio, adjustment for sex, age, BMI, regular exercise, rheumatic disease and leg injury*

§ *Meniscectomy, chondroplasty and diagnostic knee arthroscopy*

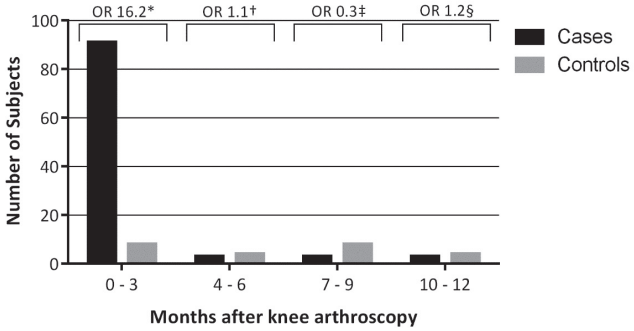

Figure 2a. *Frequency of the occurrence of events in months within one year after knee arthroscopy*

Description: Time between knee arthroscopy and occurrence of venous thrombosis is defined as difference between date of knee arthroscopy and diagnosis of venous thrombosis in the cases or the index date in the controls. All the odds ratios (OR) are adjusted for sex, BMI, regular exercise, rheumatic disease and minor leg injury.

** OR 16.2 (95CI; 7.8 – 33.7). Adjusted OR with 95% confidence interval.*

† OR 1.1 (95CI; 0.2 – 5.1). Adjusted OR with 95% confidence interval.

‡ OR 0.3 (95CI; 0.1 – 1.4). Adjusted OR with 95% confidence interval.

§ OR 1.2 (95CI; 0.3 – 5.5). Adjusted OR with 95% confidence interval.

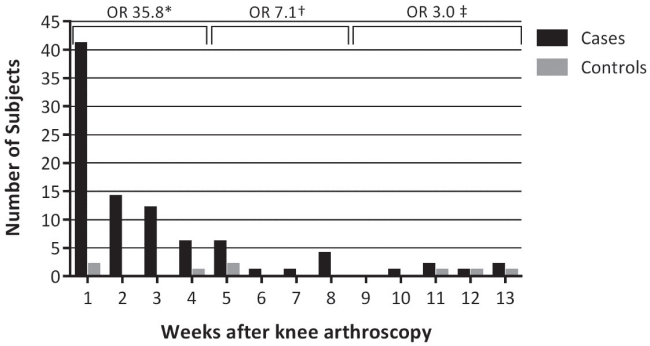

Figure 2b. *Frequency of the occurrence of events within the first 13 weeks after knee arthroscopy.*

Description: Time between knee arthroscopy and occurrence of venous thrombosis is defined as difference between date of knee arthroscopy and diagnosis of venous thrombosis in the cases or the index date in the controls. All the odds ratios (OR) are adjusted for sex, BMI, regular exercise, rheumatic disease and minor leg injury.

** OR 35.8 (95CI; 11.2 – 114.5). Adjusted OR with 95% confidence interval.*

† OR 7.1 (95CI; 3.3 – 15.6). Adjusted OR with 95% confidence interval.

Indication of arthroscopy; Genetic and acquired risk factors

Ligament reconstruction led to a higher risk of VT than regular knee arthroscopy, although not significantly (17-fold increased risk vs 5-fold increased risk for the other indications (table 2)). The risk was also clearly higher in patients who had one or more additional risk factor for venous thrombosis than in patients without (table 3). As can be seen in table 3, the use of oral contraceptives at time of arthroscopy in women below 50 years of age led to a 46-fold increased risk, relative to women with neither risk factor. No further increased risk of VT was found in obese patients who had an arthroscopy of the knee compared with non-obese patients. Carriers of the Factor V Leiden mutation, prothrombin G20210A mutation and patients with a non-O blood type taken together had an over 15-fold increased risk of venous thrombosis in the year following the arthroscopy. In addition, we found that the risk of VT strongly increased with increasing number of acquired or genetic risk factors present in combination with knee arthroscopy (from a 3-fold increased risk (ORadj 3.4; 95CI 1.4 – 8.1) when no additional risk factors were present to a 25-fold increased risk (ORadj 25.3; 95CI 8.8 – 72.9) in the presence of ≥2 more additional risk factors). Stratified by 10 years age groups we found an inverted dose response relation for age with the highest relative risk in the youngest age group (table 4).

Table 3. *Joint effect of arthroscopy of the knee and oral contraception use in women below 50 years of age, obesity, factor V Leiden, prothrombin20210 A mutation or non-O blood type and the risk of venous thrombosis within one year.*

Acquired or genetic risk factor	Knee arthroscopy	Patients	Control subjects	OR_{adj}* (95CI†)	OR_{adj}‡ (95CI†)
Oral contraception§		(n=1495)	(n=1836)		
Absent	Absent	455	1128	1 (reference)	1 (reference)
Present	Absent	1010	702	3.7 (3.2 - 4.3)	3.6 (3.1 - 4.2)
Absent	Present	7	5	3.5 (1.1 - 11.0)	3.4 (1.0 - 11.3)
Present	Present	23	1	58.4 (7.9 - 434)	46.6 (6.1 - 353)
Obesity¶		(n=4173)	(n=6044)		
Absent	Absent	3204	5221	1 (reference)	1 (reference)
Present	Absent	866	799	1.7 (1.6 - 2.0)	1.7 (1.5 - 1.9)
Absent	Present	83	20	7.1 (4.3 - 11.6)	6.5 (4.0 - 10.9)
Present	Present	20	4	7.6 (2.6 - 22.2)	7.1 (2.4 - 21.1)
Factor V Leiden**		(n=3696)	(n=4660)		
Absent	Absent	3001	4395	1 (reference)	1 (reference)
Present	Absent	597	245	3.6 (3.1 - 4.2)	3.7 (3.1 - 4.3)
Absent	Present	83	20	6.2 (3.8 - 10.1)	5.8 (3.5 - 9.5)
Present	Present	15	0	∞	∞
Prothrombin G20210 A mutation††		(n=3697)	(n=4671)		
Absent	Absent	3419	4552	1 (reference)	1 (reference)
Present	Absent	180	89	2.7 (2.1 - 3.5)	2.6 (2.0 - 3.4)
Absent	Present	95	18	7.1 (4.3 - 11.8)	6.6 (3.9 - 11.1)
Present	Present	3	2	2.0 (0.3 - 11.7)	1.7 (0.3 - 11.0
Non-O Blood type‡‡		(n=3682)	(n=4657)		
Absent	Absent	996	2122	1 (reference)	1 (reference)
Present	Absent	2588	2515	2.2 (2.0 - 2.4)	2.2 (2.0 - 2.4)
Absent	Present	28	8	7.6 (3.4 - 16.7)	6.3 (2.8 - 14.3)
Present	Present	70	12	12.7 (6.8 - 23.5)	12.3 (6.6 - 23.0)

Table 3. *Joint effect of arthroscopy of the knee and oral contraception use in women below 50 years of age, obesity, factor V Leiden, prothrombin20210 A mutation or non-O blood type and the risk of venous thrombosis within one year. (continued)*

Acquired or genetic risk factor	Knee arthroscopy	Patients	Control subjects	OR_{adj}* (95CI†)	OR_{adj}‡ (95CI†)
Factor V Leiden or Prothrombin G20210 A mutation or non-O-blood type§§		(n=3683)	(n=4649)		
Absent	Absent	804	1965	1 (reference)	1 (reference)
Present	Absent	2781	2664	2.6 (2.3 - 2.8)	2.6 (2.3 - 2.9)
Absent	Present	22	8	6.8 (3.0 - 15.4)	5.8 (2.5 - 13.3)
Present	Present	76	12	15.8 (8.6 - 29.3)	15.3 (8.1 - 28.5)
Number of risk factors present¶¶		(n=574)	(n=1498)		
0	Absent	477	1478	1 (reference)	1 (reference)
0	Present	8	6	4.5 (1.5 - 12.9)	4.2 (1.4 - 12.6)
1	Present	52	10	18.9 (9.3 - 38.4)	18.4 (8.9 - 37.9)
≥2	Present	37	4	33.5 (11.8 - 95.0)	24.7 (8.5 - 71.8)

* *ORadj: adjusted odds ratio, adjustment for sex and age*

† *95CI: 95% confidence interval*

‡ *ORadj: adjusted odds ratio, adjustment for sex, age, BMI, regular exercise, rheumatic disease and leg injury. For the analysis of obesity as risk factor adjustments are made for sex, age, regular exercise, rheumatic disease and minor leg injury.*

§ *Of the women below <50 years of age of 67 cases and 35 controls no information was available on oral contraception use.*

¶ *Obesity: Body mass index in kg/m2 >30.*

** *Of 477 cases and 1384 cases no information was available on factor V Leiden.*

†† *Of 476 cases and 1373 cases no information was available on the prothrombin G20210A mutation.*

‡‡ *Of 491 cases and 1387 cases no information was available on the blood type.*

§§*Of 490 cases and 1395 cases no information was available on Factor V Leiden, the prothrombin G20210A mutation or the blood type.*

¶¶ *Presence of any of the risk factors oral contraception, obesity, Factor V Leiden, Prothrombin G20210A mutation and Non-O blood type. Of 289 cases and 1320 cases no information was available on at least one risk factor. 3310 cases and 3226 controls had no arthroscopy of the knee and at least one risk factor present*

Table 4. *Knee arthroscopy and the risk of venous thrombosis within one year for different age categories.*

	Knee arthroscopy		No orthopedic surgery			
Age	Patients (n=103)	Control Subjects (n=24)	Patients (n=4070)	Control Subjects* (n=6018)	ORadj† (95CI‡)	ORadj§ (95CI‡)
18 – 29	12	1	461	693	18.8 (2.4 - 148.9)	14.1 (1.7 - 113.7)
30 – 39	31	5	754	1229	12.1 (4.7 - 31.4)	13.1 (4.9 - 34.6)
40 – 49	31	6	976	1459	8.1 (3.4 - 19.8)	6.4 (2.6 -15.9)
50 – 59	19	7	998	1605	4.2 (1.8 - 10.2)	4.0 (1.6 -9.7)
60 – 69	10	5	881	1032	2.5 (0.8 - 7.4)	2.5 (0.8 - 7.4)

***** *Two control subjects were above 70 years of age.*

† OR_{adj}*: adjusted odds ratio, adjustment for sex*

‡*95CI: 95% confidence interval*

§ OR_{adj}*: adjusted odds ratio, adjustment for sex, BMI, regular exercise, rheumatic disease and leg injury*

Discussion

Knee arthroscopy is associated with a strongly increased risk of VT. In the three-month period following the procedure we found a 16-fold increased risk. A higher risk was found for arthroscopic ligament reconstructions than for the less invasive meniscal surgeries, diagnostic arthroscopies or chondroplasties. Patients who had knee arthroscopy in combination with well-known acquired or genetic risk factors (oral contraceptives, Factor V Leiden, prothrombin G20210A mutation or non-O blood group) had an additionally increased risk. These distinct differences in risk in patients with well-known risk factors indicate that high risk groups can be identified on the basis of the presence of one or more risk factor for VT.

Comparison with literature

Some information is available in the literature on the effect of the presence of additional risk factors for VT. Increasing age (≥ 30 or ≥50 years), oral contraceptive use, female sex, previous DVT, history of cancer and tourniquet time > 60 minutes or increased operating time (≥90 minutes) have previously been reported to be associated with an additionally increased risk.[21-25] In contrast to the reported higher risk for increasing age we found an inverse dose response relation for the relative risk of VT per 10-years age strata (i.e. the highest relative risk in the youngest age group). Because the baseline risk of VT is lowest in the youngest age group,[3] the relative risk will be most increased for the youngest ages when the additional absolute risk through arthroscopy is the same per age group. Another possible explanation is the use of oral contraceptives by women in the younger age groups. Because of the limited number of control subjects with a knee arthroscopy we could not stratify additionally on sex and oral contraceptive use to analyze this.

We found a higher risk of VT for ligament reconstruction compared to regular knee arthroscopies. Previous studies did not find a difference in thrombosis risk for these patients.[23,24,26] In one prospective cohort study, however, a high risk of symptomatic VT (4% in 8 weeks) after anterior cruciate ligament reconstruction was reported, while the same investigators reported a risk of 0.9% in a 8 weeks after regular knee arthroscopy.[27,28]

None of the previous studies reported on the combination of genetic risk factors and knee arthroscopy and risk of VT. In addition, no earlier study reported on the time

relation between arthroscopy and occurrence of thrombosis, which relation we found to be clearly present.

Mechanisms

In contrast to other orthopedic surgeries, tissue damage is usually negligible during knee arthroscopy and the duration of the procedure is usually short (generally around 30 minutes).[27] A possible explanation for the increased risk could be the use of a tourniquet during the procedure resulting in stasis of blood flow and hypoxia of the leg. Hypoxia leads to an inflammatory reaction, coagulation activation and thrombin formation.[29] In total knee arthroplasty the use of a tourniquet resulted in higher postoperative local and systemic levels of thrombin- antithrombin complexes (TAT), plasmin antiplasmin complex (PAP), prothrombin fragment 1+2 (F12) and D-dimer than in knee arthroplasties without tourniquet use.[30-33] Further, the risk of venous thrombosis after arthroscopy can be partially increased because of a prior leg injury.[34] However the risk of venous thrombosis attenuated only slightly after correcting for this risk factor. We found a higher risk for DVT of the leg after knee arthroscopy than for PE. The RR(PE) divided by the RR (DVT) is below 1, indicating that knee arthroscopy is a risk factor with a stronger effect for DVT of the leg than for PE.[35] This can possibly be explained by the local stasis of blood-flow and the hypoxia in the leg caused by tourniquet use. The higher risk we found for patients who had arthroscopic ligament reconstruction vs. meniscectomy, diagnostic arthroscopy and chondroplasty, can possibly be explained by its more extensive tissue damage and the longer duration of surgery resulting in increased tourniquet time and hypoxia of the leg.

Limitations

A limitation of this study was that we did not have information on the use of thromboprophylaxis around the procedure. If we look at the results of a survey on thromboprophylaxis held in the Netherlands in 2002, which was carried out in the same period as the inclusion period of our study, 71% of orthopedic surgeons provided thromboprophylaxis after knee arthroscopy. However, 91% of these surgeons administered only a single dose of prophylaxis (usually low molecular weight heparin (LMWH)).[36] The prophylactic effect of a single dose of LMWH is not known for this indication but is likely to be small. Nevertheless, a few events may have been prevented, which would have led to an underestimation of the true risk of VT in these patients. Furthermore, we do not have information on the side on which the knee arthroscopy

was performed. Therefore, we cannot analyze if the VT event occurred in the same leg as the arthroscopy. Another limitation in our study is that the number of subjects in subgroups were sometimes small so we had to use one-year time windows for the subgroup analyses. This has led to an underestimation of the risk of VT in these high-risk groups, since the VT risk of these fixed risk factors stays constant over time, while the risk of arthroscopy of the knee diminishes over the year. Nevertheless, these results still show that the risk of VT after arthroscopy is additionally increased in patients who have other risk factors, which can alert clinicians that certain patients are at particularly high risk, i.e. at least of the size described in table 3.

In addition, recall bias can play a role in case control studies. However, knee arthroscopy, like surgery in general, has a high impact on patients, and it is therefore unlikely that recall of having had a knee arthroscopy would differ between cases and controls. Lastly, we were only able to calculate estimates of the relative risk using the odds ratio (due to the case-control design of our study) and no incidence rates. We can, however, give a rough indication of the absolute risk of VT after knee arthroscopy. Based on an incidence of 0.75 per 1000 person-years in the general population in the age group included in our study (18-69 years)),[3] a 16-fold increased risk in three months corresponds to an estimated absolute risk of venous thrombosis of 0.3% in three months.

Clinical implications

Because knee arthroscopy is such a frequently performed procedure (estimated at 4 million arthroscopies each year worldwide),[13] the absolute number of thrombotic events will be high. Identification of high-risk patients can optimize prophylactic treatment; i.e. high-risk patients can benefit from anticoagulant treatment while patients with low intrinsic risk will not unnecessarily be exposed to the bleeding risk. We have shown that there is a distinct difference in risk for VT between individuals. Knowledge on the effects of other risk factors for VT, such as malignancy and family history of VT is needed and can be used to develop prediction models for VT risk. The impact of these models on the reduction of the occurrence of VT needs to be established in further studies.[37,38]

Conclusion

We observed a strongly increased risk of venous thrombosis after knee arthroscopy. Furthermore, we found an additionally increased risk for patients with ligament reconstructions and for patients with additional acquired or genetic risk factors.

Our results show that there are distinct differences in thrombosis risk per person. Further studies should be aimed at demonstrating the benefits of individualization of prophylactic treatment. Considering the high frequency of knee arthroscopy, this may reduce thrombosis morbidity.

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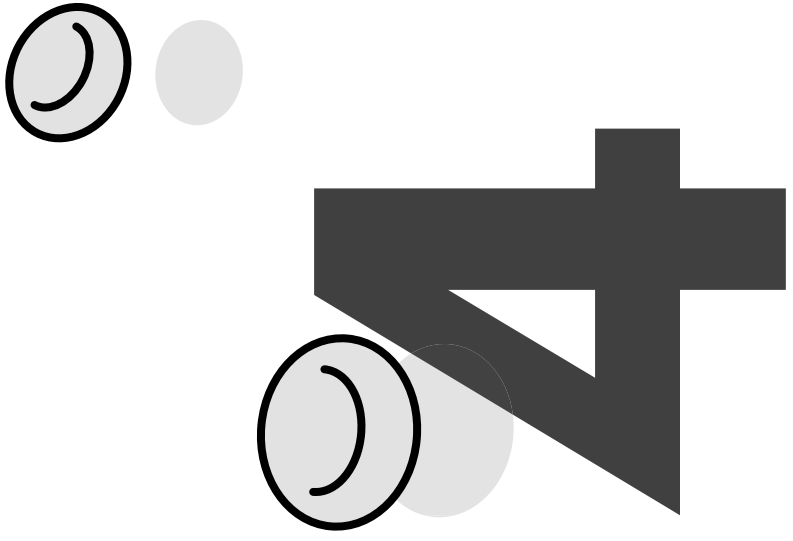
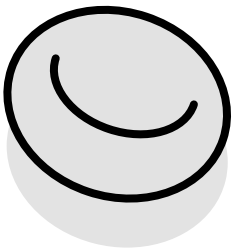
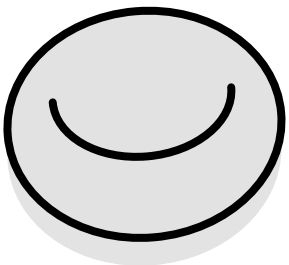
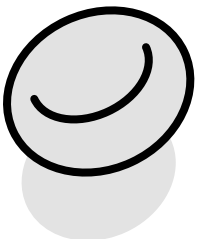


CHAPTER

Thromboprophylaxis for lower leg cast immobilization and knee arthroscopy: a survey study







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Abstract

Background

The effect of prophylaxis on the prevention of symptomatic venous thrombosis in patients with lower leg cast immobilization or after knee arthroscopy is not clear. Our aim was to assess the current practice of thrombosis prophylaxis in Dutch hospitals and to determine considerations for prescribing prophylaxis.

Methods

Electronic questionnaires were sent to all orthopedic (90) and trauma surgery departments (89) and orthopedic clinics (16) in the Netherlands regarding thrombosis prophylaxis in patients with lower leg cast immobilization or after knee arthroscopy.

Results

Response rate was 88% for orthopedic surgery departments/clinics and 81% for trauma surgery departments. At the large majority of departments, prophylaxis is provided for both indications. Only at 3 (4%) orthopedic and 3 (4%) trauma surgery departments this was not the case for lower leg cast immobilizations and at 10 (11%) orthopedic surgery departments not for knee arthroscopies. Substantial differences in prophylactic strategies were observed, dependent on the indication for treatment and on the presence of concomitant risk factors for venous thrombosis. Most reported considerations for prescribing prophylaxis were: the perceived risk reduction of prophylaxis outweighs the bleeding risk; the experience that prophylaxis is effective; to act in accordance with hospital guidelines.

Conclusion

Despite insufficient evidence of its effect, thrombosis prophylaxis is administered to the large majority of patients with lower leg cast immobilization and after knee arthroscopy. However, depending on the indications, large variations in prophylaxis strategies exist. Uniform prophylactic treatment, based on good quality evidence, is needed to improve quality of care of these patients.

Introduction

The effect of thrombosis prophylaxis on prevention of symptomatic venous thrombosis for two of the most commonly performed orthopedic treatments world-wide, i.e. lower leg cast immobilization and arthroscopy of the knee is not well established, nor is the cost-effectiveness of this treatment.[1-14] In this survey study we aimed to provide insight in the thrombosis prophylaxis policies of orthopedic and trauma surgeons with respect to these indications and in their considerations for providing such therapy.

Venous thrombosis (i.e. deep vein thrombosis and pulmonary embolism) occurs in about 1-2 per 1000 persons per year in the general population and is a serious condition leading to chronic morbidity (e.g. post thrombotic syndrome and pulmonary hypertension) and an increased risk of mortality.[15-19] The risk of venous thrombosis is increased after surgery, and is particularly high after orthopedic surgery (estimated 4% in 35 days after major orthopedic surgery).[3;20;21] Because of this high risk, thrombosis prophylaxis is recommended for these patients.[3;4;8] However, for lower leg cast immobilization and knee arthroscopy the risk of venous thrombosis and the effect of prophylactic therapy are not well known, for the following reasons: The less clinically relevant endpoint 'asymptomatic venous thrombosis' was used as primary end point in trials regarding these patients and these trials were underpowered to draw conclusions on the effect of prevention of symptomatic events.[1-14] Furthermore, the risks of symptomatic events were most likely overestimated in these trials because of the inclusion of patients with complete leg cast immobilization and patients with arthroscopic assisted ligament reconstructions. These patients have more extensive trauma and more extensive surgery and are therefore expected to have a higher risk of venous thrombosis.[22-26] In addition, when providing anticoagulant treatment, the risk of complications, such as bleeding, needs to be taken into account.[3;4;8;24] For these reasons, both national and international guidelines are reluctant in advising in favor of thrombosis prophylaxis for these patients and recommend not to use routine prophylaxis, to use prophylaxis only in patients with an increased risk for venous thrombosis (e.g. longer duration or more extensive surgery or in patients with additional risk factors) or leave it to the clinician to decide whether to provide prophylactic treatment.[3;4;8]

Despite this lack of evidence, and hence, somewhat indefinite guidelines, 70% of orthopedic and trauma surgeons provided thrombosis prophylaxis to patients with lower leg cast immobilization and 71% of orthopedic surgeons did so for patients who

underwent knee arthroscopy in the Netherlands in 2007.[27] Reasons for this large scale use of thrombosis prophylaxis are unknown.[27-29] From clinical experience, we believed that the proportion of surgeons that provides prophylaxis to these patients had increased since. Therefore, the aim of this survey study was to obtain insight in the thrombosis prophylaxis policies of orthopedic and trauma surgeons with respect to patients with lower leg cast immobilization or who underwent arthroscopy of the knee and in their considerations for providing such therapy to these patients.

Materials and methods

In July 2013, a digital survey (NetQuestionnaires, version 6.0, NetQuestionnaires Netherlands B.V, Utrecht, the Netherlands) was sent to all departments of orthopedic surgery (90 hospital departments and 16 private orthopedic clinics) and all departments of surgery (89 hospital departments (89 instead of 90 because in one hospital lower leg trauma is exclusively treated by orthopedic surgeons) in the Netherlands. The survey concerned thrombosis prophylaxis policy in patients with lower leg cast immobilization and patients who underwent arthroscopy of the knee. Careful attention was put into designing unambiguous and non-leading questions and answer options. [30;31] A link to the survey was included in a personalized e-mail sent on behalf of the heads of the (sub) departments of orthopedic surgery and trauma surgery (RGHHN and IBS) of the Leiden University Medical Center. The survey was sent to one orthopedic surgeon and one trauma surgeon for every hospital department or private clinic. Trauma surgeons were selected based on their registration as trauma surgeon and orthopedic surgeons based on their registration as orthopedic surgeon and/or lower extremity or knee surgeon. If surgeons did not respond, two reminders were sent. When surgeons did not reply after two reminders another orthopedic or trauma surgeon from the same department or clinic was contacted.[32]

For orthopedic surgeons working in hospitals, the survey regarded the thrombosis prophylaxis policy in patients with lower leg cast immobilization and around arthroscopies of the knee. For orthopedic surgeons working in a private clinic, only questions regarding arthroscopy of the knee were included. Trauma surgeons were asked about the thrombosis prophylaxis policy in patients with lower leg cast immobilization.

All data were analyzed anonymously using SPSS version 20.0.0 (IBM, Armonk, New York, US). For knee arthroscopy, the results of the hospital departments and orthopedic private clinics were combined, as these results were similar. For lower leg cast immobilization, the data were separately analyzed for orthopedic and trauma surgeons. Answers to open questions were categorized. Categorical data were expressed as proportions using percentages.

Results

The survey was completed at 93 of the 106 contacted departments of orthopedic surgery (79 hospital departments (88%) and 14 orthopedic private clinics (88%)). From the departments of trauma surgery, the response rate was 81% (72 of 89 departments completed the questionnaire). Of these departments, 69 (96%) trauma surgery and 70 (89%) orthopedic surgery departments had a protocol regarding thrombosis prophylaxis in patients with lower leg cast immobilization. For knee arthroscopy patients, 84 (90%) of orthopedic surgery departments had a thrombosis prophylaxis protocol. The majority of these protocols was based on the guideline of the Dutch institute for healthcare improvement (CBO) (table 1).

Thrombosis prophylaxis

At the large majority of departments, thrombosis prophylaxis is prescribed. At only 3 (4%) of the 72 trauma surgery departments and 3 (4%) of the 79 orthopedic surgery departments thrombosis prophylaxis is not provided at all to patients with lower leg cast immobilization. At the other departments, the decision to provide prophylactic treatment is dependent on whether patients are allowed to bear weight and the combination of cast immobilization with surgical treatment (table 2).

***Table 1**. Guidelines used as basis for department or hospital protocols.*

Guideline used	Lower leg cast		Knee arthroscopy
	Trauma surgery (n=72), n (%)	Orthopedic surgery (n=79), n (%)	Orthopedic surgery (n=93), n (%)
No protocol	3 (4)	9 (11)	9 (7)
Not based on a guideline*	15 (21)	12 (15)	13 (14)
CBO†/NOV‡	29 (40)	34 (43)	45 (48)
CBO†/NOV‡+AAOS§	3 (4)	4 (5)	3 (3)
CBO†/NOV‡+ACCP¶	3 (4)	0 (0)	2 (2)
CBO†/NOV‡+AAOS§+ACCP¶	1 (1)	2 (3)	0 (0)
CBO†/NOV‡+AAOS§+ACCP¶+CDER**	0 (0)	0 (0)	1 (1)
AAOS§	1 (1)	1 (1)	2 (2)
ACCP¶	2 (3)	0 (0)	0 (0)
AAOS§+ACCP¶	0 (0)	0 (0)	1 (1)
Not known by respondent	15 (21)	17 (22)	17 (18)

** Predominantly Cochrane review regarding this subject or own review of the literature*

† CBO: Centraal Begeleidings Orgaan: Dutch institute for healthcare improvement

‡ NOV: Dutch Orthopedic Society. The NOV refers to the CBO guideline for thrombosis prophylaxis in orthopedic surgery patients

§ AAOS: American Academy of Orthopedic Surgeons

¶ ACCP: American College of Chest Physicians

***CDER: Cardiovascular Disease Education and Research Trust*

***Table 2.** Thrombosis prophylaxis policies for patients with lower leg cast immobilization*

Type of treatment	Always		Risk factors*		Never†	
	Trauma Surgery (n=72), n (%)	Orthopedic Surgery (n=79), n (%)	Trauma Surgery (n=72), n (%)	Orthopedic Surgery (n=79), n (%)	Trauma Surgery (n=72), n (%)	Orthopedic Surgery (n=79), n (%)
Conservative						
Non-weight bearing	57 (79%)	50 (63%)	11 (15%)	26 (33%)	4 (6%)	3 (4%)
Weight bearing	52 (72%)	46 (58%)	14 (19%)	27 (34%)	6 (8%)	6 (8%)
Surgical						
Non-weight bearing	51 (71%)	63 (80%)	17 (24%)	13 (16%)	4 (6%)	3 (4%)
Weight bearing	54 (75%)	56 (71%)	13 18%)	18 (23%)	5 (7%)	5 (6%)

** Thrombosis prophylaxis is only provided to patients with additional risk factors for venous thrombosis.*

† On 3 (4%) trauma surgery and 3(4%) orthopedic surgery departments thrombosis prophylaxis is never provided to patients, irrespective of the indication of cast immobilization.

Knee arthroscopy patients never receive prophylactic treatment at 10 (11%) of the 93 orthopedic surgery departments. In departments that do provide prophylactic therapy, the decision to prescribe prophylaxis is highly dependent on the indication for knee arthroscopy (table 3). Furthermore, for both indications, giving prophylactic treatment is influenced by the presence of additional risk factors for venous thrombosis (table 4), the presence of risk factors for bleeding and the use of co-medications that influence the coagulation system, such as non-steroidal anti-inflammatory drugs and platelet aggregation inhibitors.

Table 3. *Thrombosis prophylaxis policies for knee arthroscopy*

Type of knee arthroscopy	Orthopedic Surgery (n=93)		
	Always, n (%)	**Risk factors*, n (%)**	**Never, n (%)**
Diagnostic	30 (32%)	39 (42%)	24 (26%)
Loose body removal	30 (32%)	40 (43%)	23 (25%)
(Partial) meniscectomy	30 (32%)	39 (42%)	24 (26%)
Microfracture surgery	39 (42%)	34 (37%)	20 (22%)
Meniscal suture	48 (52%)	26 (28%)	19 (20%)
ACL† reconstruction	72 (77%)	11 (12%)	10 (11%)

** Thrombosis prophylaxis is only provided to patients with additional risk factors for venous thrombosis.*

† ACL: anterior cruciate ligament

Table 4. *Risk factors for venous thrombosis in the presence of which thrombosis prophylaxis is provided in patients with below knee cast immobilization or after knee arthroscopy*

Risk factors for thrombosis	Trauma surgery (n=23), n (%)	Orthopedic surgery (n=68), n (%)
Cardiovascular disease	4 (17%)	15 (22%)
Family history of thrombosis or hereditary thrombophilia	18 (78%)	45 (66%)
Hospitalization	6 (26%)	16 (24%)
Hormonal contraception use	14 (61%)	31 (46%)
Hormonal replacement therapy use	6 (26%)	9 (13%)
Infectious disease	1 (4%)	2 (3%)
Malignancy	17 (74%)	26 (38%)
Renal insufficiency	0 (0%)	1 (1%)
Obesity (BMI>30)	17 (74%)	28 (41%)
Recent surgery	4 (17%)	6 (9%)
Smoking	9 (39%)	32 (47%)
Previous episode of venous thrombosis	22 (96%)	61 (90%)
Female gender	6 (26%)	13 (19%)
Pregnancy	6 (265)	9 (13%)
Other*	2 (9%)	6 (9%)

**Immobilization, combination of risk factors (predominant oral anticonception use and smoking), age>16 years, age>75 years, previous vascular surgery*

Type of thrombosis prophylaxis

The prophylactic treatment of choice for patients with lower leg cast immobilization is low molecular weight heparin (LMWH) at 67 trauma surgery departments (97%) and 74 orthopedic surgery departments (97%). The most commonly used low-molecular weight heparin is nadroparin. For knee arthroscopy, at all departments of orthopedic surgery that provide prophylaxis, LMWH is used (83 (100%)), once again most commonly nadroparin (table 5).

Table 5. *Thrombosis prophylaxis of choice*

Type of prophylaxis	Lower leg cast		Knee arthroscopy
	Trauma surgery (n=72), n (%)	Orthopedic surgery (n=79), n (%)	Orthopedic surgery (n=93), n (%)
LMWH*	67 (93%)	74 (94%)	83 (89%)
Nadroparin	43 (64%)	51 (69)	54 (65%)
Dalteparin	19 (28%)	17 (23%)	21 (25%)
Enoxaparin	5 (8%)	5 (7%)	6 (7%)
Not specified	0 (0%)	1 (1%)	2 (2%)
LMWH* + VKA†	0 (0%)	1 (1%)	0 (0%)
VKA†	1 (1%)	1 (1%)	0 (0%)
Fondaparinux	1 (1%)	0 (0%)	0 (0%)
No prophylaxis	3 (4%)	3 (4%)	10 (11%)

***** *LMHW: Low molecular weight heparin*

† *VKA: Vitamin K antagonist*

Duration of prophylaxis

In patients with lower leg cast immobilization, prophylactic treatment is almost always provided for the duration of immobilization (trauma surgery departments 66 (96%) and orthopedic surgery departments 68 (89%). At the other departments, prophylaxis is provided during hospital stay, for a fixed period of time or for the period of cast-immobilization plus one week thereafter.

For knee arthroscopy patients the duration of prophylaxis ranges from 1 day to six weeks and strongly depends on the indication for the knee arthroscopy. Furthermore, the duration of prophylactic treatment per indication varies widely between hospitals (figure 1).

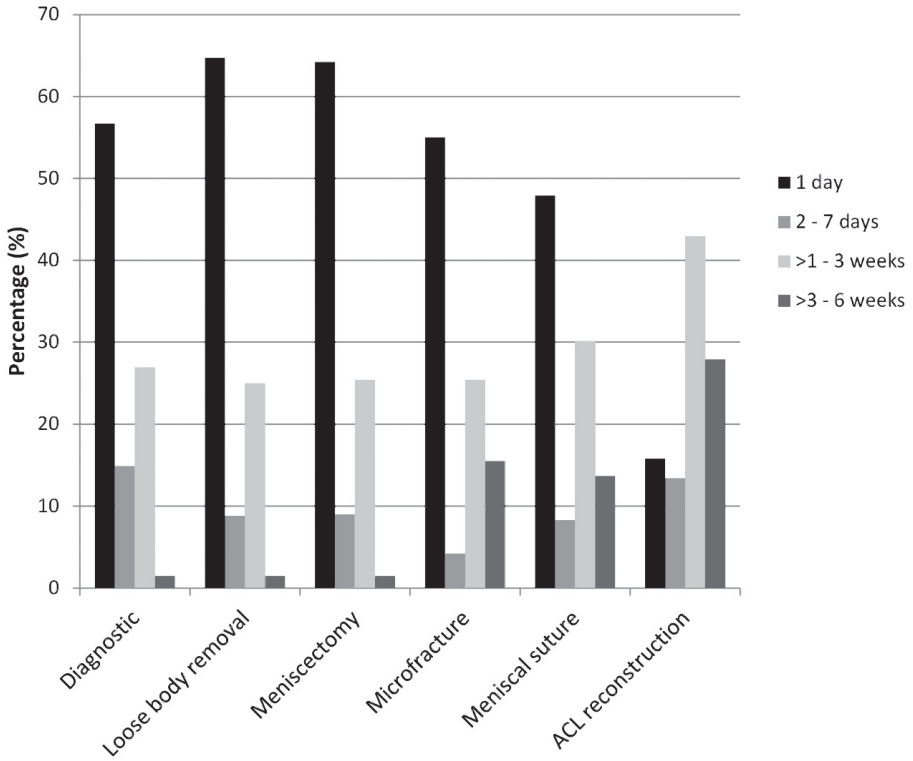

Figure 1. *Duration of thrombosis prophylaxis for different types of knee arthroscopies.*
Description: The graph shows the percentages of orthopedic surgeons that provide thrombosis prophylaxis for 1 day, 2 – 7 days, >1 – 3 weeks or >3 – 6 weeks for different types of knee arthroscopies. ACL reconstruction is anterior cruciate ligament reconstruction.

Reasons for thrombosis prophylaxis

Considerations to prescribe prophylactic therapy are that clinicians assume that the risk reduction for thrombosis outweighs the bleeding risk; their experience that prophylaxis is effective; and that clinicians act in accordance with their department or hospital protocol (table 6).

Table 6. *Reasons for providing thrombosis prophylaxis*

Reason	Lower leg cast		Knee arthroscopy
	Trauma surgery (n=72), n (%)	Orthopedic surgery (n=79), n (%)	Orthopedic surgery (n=93), n (%)
Prophylaxis	69 (96%)	n=76 (96%)	83 (89%)
Reduced thrombosis risk outweighs bleeding risk	45 (65%)	49 (64%)	30 (36%)
Clinical experience shows prophylaxis is effective	17 (25%)	19 (25%)	9 (11%)
Negative experience without prophylaxis	0 (0%)	1 (1%)	3 (4%)
Risk of complications of prophylaxis considered very small	0 (0%)	0 (0%)	2 (2%)
Act in accordance with hospital or department protocol	52 (75%)	54 (71%)	48 (58%)
No prophylaxis	3 (4%)	3 (4%)	10 (11%)
No clear scientific evidence for efficacy	2 (67%)	3 (100%)	7 (70%)
Clinical experience shows prophylaxis is not effective	0 (0%)	0 (0%)	2 (20%)
Act in accordance with hospital or department protocol	2 (67%)	2 (67%)	6 (60%)

Choice for type of thrombosis prophylaxis

The most important reason for LMWH as prophylactic treatment of choice in patients with lower leg cast immobilization is that this is in accordance with hospital or department protocol in 54 trauma surgery (81%) and 57 orthopedic surgery departments (77%). In addition, in 28 trauma surgery (42%) and 29 orthopedic surgery departments LMWH is considered the most safe prophylactic treatment, in 19 (28%) trauma surgery and 29 (39%) orthopedic surgery departments it is preferred because of extensive clinical experience and in 15 trauma surgery (22%) and 14 orthopedic surgery departments (19%) it is considered to be the most effective prophylactic treatment.

Reasons for the preference for LMWH as prophylactic treatment around knee arthroscopies is that it is in accordance with the department or hospital protocol at 49 (59%) departments; LMWHs are considered the most safe option at 47 (57%) of departments; LMWHs are considered to be the most effective option at 28 (34%) of departments and at 25 departments (30%) LMWHs are preferred because of extensive clinical experience with this type of anticoagulants.

Discussion

In this survey study, we were able to give a detailed and, considering the high response rate, reliable overview of current thrombosis prophylaxis policies in the Netherlands for patients with lower leg cast immobilization and for patients who had a knee arthroscopy. Despite insufficient evidence on the effect of prophylaxis on the prevention of symptomatic events and on its cost-effectiveness, prophylaxis is prescribed in the large majority of clinical practices. Furthermore, we found substantial differences in prophylactic strategies between departments depending on the indication for below-knee cast immobilization or knee arthroscopy and on the presence of additional risk factors for venous thrombosis. The most important reasons to provide prophylactic treatment were the assumption that the risk reduction for thrombosis outweighs the bleeding risk; that clinicians have the experience that prophylaxis is effective; and that clinicians act in accordance with department or hospital protocol by providing prophylaxis.

In trials regarding thrombosis prophylaxis in patients with below knee cast immobilization or undergoing knee arthroscopy, asymptomatic venous thrombosis has generally been used as primary endpoint. The incidences of these events in the control groups of the trials varied between 0 – 15.6% for knee arthroscopy (follow up 1 week to 3 months) and between 4.3 and 36% during 4 – 6 weeks of cast immobilisation.[1;2;5-7;9-14] However, these trials were underpowered to draw conclusions on the prevention of symptomatic venous thrombosis, because the risks of these events were much lower (between 0 – 2.5% for knee arthroscopy and 0 – 5.5% for cast immobilization).[3;4;8] The risks of these symptomatic events are furthermore not representative for below knee cast immobilization and regular knee arthroscopies because of the inclusion of patients with more extensive trauma or surgery (complete leg cast and ligament reconstructions).

Because of this, a balance between the benefit (prevention of symptomatic events) and risk of complications, such as bleeding events, could not be established.

This lack of evidence is reflected in the variations in guideline recommendations. The guideline of the American College of Chest Physicians recommends no prophylaxis while the guideline of the National Institute for Clinical Excellence (United Kingdom) recommends to consider prophylaxis in the presence of additional risk factors.[3;4] Furthermore, the guideline of the Dutch institute for healthcare improvement (CBO) gives no definite recommendation for patients with lower leg cast immobilization. For knee arthroscopy in general it recommends no prophylaxis, however for reconstructive surgery or in patients with additional risk factors prophylaxis can be considered.[8] Considering that the majority of department protocols are based on the CBO guideline, the variation in treatment strategies in the Netherlands may be explained by the fact that these guidelines can be interpreted in several ways, which is again due to the lack of evidence in the literature.

In comparison with previous survey studies, a further increase in the use of thrombosis prophylaxis was seen. For lower leg cast immobilization, the proportion of departments where prophylaxis is never prescribed further decreased from 50% in 2002 and 30% in 2007 to only 4% in 2013.[27-29] For knee arthroscopy the proportion of departments that never use prophylaxis decreased from 40% in 2002 and 48% in 2007 to 11% in 2013.[27;28] In addition, there are international differences. For example, in the United Kingdom in 2010, only at 16% of the orthopedic surgery departments prophylaxis was routinely provided to patients with lower leg plaster cast.[33] In Italy, already in 2004, 94% of orthopedic surgery departments provided thrombosis prophylaxis around knee arthroscopies.[34]

When interpreting our results, some limitations need to be taken into account. In this study, we assessed the prophylaxis policies at department but not at individual physician level. The response of the single individual surgeon does not necessarily have to be representative for the department. However, the vast majority of orthopedic surgery departments (89% for lower leg cast immobilization and 90% for knee arthroscopy) and trauma surgery department (96%) have a protocol regarding thrombosis prophylaxis in these patients. We expect that any variation within departments will therefore be small. Furthermore, the response rate of our study is not 100%. However, our response rates

of 81% and 88% are still high and well above the 70% needed to limit non-response bias.[35;36] In addition, a non-validated survey was used. Furthermore, as in most survey studies, there is a risk of the respondent answering what he or she feels is appropriate rather than true. Because of this, particular attention was put into the design of non-leading and unambiguous questions and answers.[30;31]

While we can only speculate about possible explanations for the further increasing use of thrombosis prophylaxis over the last years, it could be that defensive medicine has become more predominant over evidence-based medicine. However, this large-scale use of thrombosis prophylaxis without a proper scientific basis for a beneficial effect may have medico-legal implications for involved clinicians, especially when (bleeding) complications occur. Although the bleeding risk with LMWH is perceived to be low, the absolute number of bleedings can be high since both knee arthroscopy and lower leg cast immobilizations are such frequent procedures.

Our results indicate that there is a clear need for good quality research. Uniform prophylactic treatment across hospitals is needed in order to improve the quality of care of patients. Instead of focusing on asymptomatic venous thrombosis, the primary end point of new studies should be symptomatic venous thrombosis.[3;24] In addition, complications of prophylactic therapy, such as bleeds, need to be taken into account in order to establish a benefit-risk ratio. For cast immobilization, only patients with lower leg cast immobilization should be included and for knee arthroscopy there is a need for trials with better stratification in type of arthroscopy.[24] Furthermore, identification of high-risk groups is needed, which can lead to individualized prophylactic therapy in order to optimize the benefits and risks from anticoagulant therapy.[3]

Conclusion

Thrombosis prophylaxis is given at the large majority of orthopedic and trauma surgery departments in the Netherlands to patients with lower leg cast immobilization and around knee arthroscopies, despite insufficient evidence for a beneficial effect. Large variations are found in prophylaxis strategies between departments for different types of indications for lower leg cast immobilization and arthroscopy of the knee. Uniform prophylactic treatment across hospitals, based on good quality evidence, is needed to improve the quality of care of these patients.

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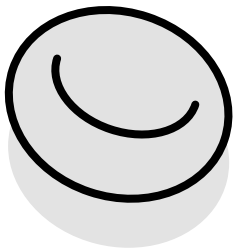
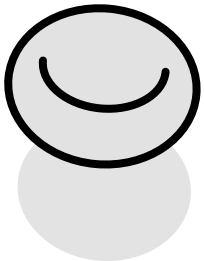
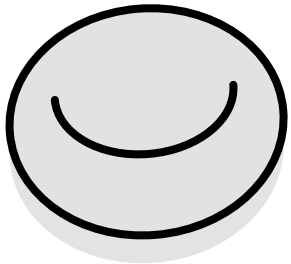
CHAPTER

Prevention of venous thromboembolism during lower leg cast immobilization: a randomized controlled trial







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Abstract

Background

Patients who need lower leg cast immobilization have an increased risk for developing venous thromboembolism. From previous trials that studied the efficacy of anticoagulant therapy an overall risk-benefit balance could not be established. Therefore, guidelines have been reluctant to recommend anticoagulant treatment.

Methods

We conducted a pragmatic, multicenter, randomized, controlled, open label, blinded endpoint trial in which patients with lower leg cast immobilization, with or without surgery, were randomly assigned to receive either low-molecular-weight-heparin (LMWH), 2850 IU (or 5700 IU in patients >100 kilograms) once daily, for the entire immobilization period, or no therapy. The primary outcome was the occurrence of symptomatic venous thromboembolism within three months following lower leg cast immobilization and the primary safety outcome was the occurrence of major bleeding within this time frame.

Results

1519 patients were enrolled, of whom 761 were randomly assigned to LMWH and 758 to no treatment. 1435 patients were included in the intention-to-treat analysis. A venous thromboembolic event occurred in 10/719 (1.4%) patients in the LMWH group and in 13/716 (1.8%) patients in the no therapy group, for a relative risk with LMWH of 0.8; 95% confidence interval (CI) 0.3 to 1.7; (risk difference -0.4%; 95% CI –1.7 to 0.9). No major bleeding event occurred.

Conclusion

In patients with lower leg cast immobilization, with or without additional surgery, thromboprophylaxis with daily LMWH during immobilization was not effective for the prevention of symptomatic venous thromboembolism. These results do not support routine thromboprophylaxis in these patients.

Introduction

Patients who are treated with lower leg cast immobilization have an increased risk for developing venous thromboembolism (VTE) (i.e. deep vein thrombosis [DVT] or pulmonary embolism [PE]).[1] Such patients therefore often receive anticoagulant therapy to prevent this. However, the magnitude of the risk for VTE following cast immobilization has not been reliably estimated (varies in studies between 0% and 5.5%)[2-5] and it is unknown whether the risks of major bleeding outweigh the benefits of treatment. In a Cochrane review, six small trials have been summarized in an attempt to answer the question if anticoagulant therapy is effective in these patients.[6] Most of these trials studied the occurrence of asymptomatic thrombosis as primary outcome in order to reduce the required sample size, and were therefore underpowered to draw conclusions on the prevention of symptomatic events. An overall risk-benefit balance could not be established and therefore international guidelines have been reluctant to advise in favor or against anticoagulant treatment in these patients.[7]

The Prevention Of Thrombosis after CAST Immobilization [POT-CAST] trial was therefore set up to compare anticoagulant treatment (Low Molecular Weight Heparin [LMWH]) with no therapy for the prevention of symptomatic VTE in patients treated with lower leg cast immobilization. We hypothesized that treatment with anticoagulants during the complete period of cast immobilization was effective for the prevention of symptomatic VTE and that this benefit outweighed the bleeding risk.

Methods

Study oversight and design

The POT-CAST trial is a prospective, multicenter, randomized, controlled, open label, blinded endpoint trial comparing two treatment strategies, i.e., one by which the anticoagulant LMWH is administered during immobilization versus one by which it is not, in patients treated with lower leg cast immobilization. The POT-CAST study was designed as a pragmatic trial to achieve maximal generalizability. The trial protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center; no methodological changes were made after approval. The POT-CAST trial was funded by The Netherlands Organization for Health Research and Development (project number 171102001) which had no role in the study design, analysis or preparation of the manuscript. The trial was registered at clinicaltrials.gov, number: NCT01542762. All

authors of the study group vouch for the accuracy and completeness of the reported data.

Participants

The POT-CAST trial was performed in eight hospitals in the Netherlands (seven teaching hospitals and one tertiary academic medical center, listed in the Supplementary Appendix). All patients, aged 18 years or older, presenting at the emergency department, who were treated with lower leg cast immobilization (no polytrauma) for at least one week were eligible for inclusion. Patients who underwent surgery of the lower leg before or after cast immobilization were also included. Exclusion criteria were a history of VTE, contra-indication for the use of LMWH (e.g. recent major bleeding), pregnancy and another indication for current use of anticoagulant therapy (either LMWH, vitamin K antagonists or direct oral anticoagulants) such as atrial fibrillation. Furthermore, patients with insufficient knowledge of the Dutch language, mental or physical disability to fulfil study requirements and patients who had already participated in the trial (for a previous cast) were excluded. All participants provided written informed consent.

Study procedures and intervention

Eligible patients were randomly assigned to receive either no treatment or a prophylactic dosage of LMWH (type of LMWH according to the hospitals preference, i.e. nadroparin or daltparin) once daily for the entire period of immobilization. The first dose was administered at the emergency department after randomization. Nadroparin 2850 IU subcutaneous or dalteparin 2500 IU subcutaneous was used for patients weighing less than 100kg, whereas patients over 100kg received a double dose.

Patients received an information leaflet for signs and symptoms of VTE and were advised to seek medical care if such symptoms arose. Follow-up started from the day of cast application for a period of 3 months as the risk for VTE returns to baseline after this period.[8] In addition to regular hospital visits, digital (online) or postal questionnaires on study compliance (e.g. duration of plaster cast), study outcomes, and study medication adherence were sent 3 and 7 weeks after cast application. In addition, patients were requested to complete a questionnaire on risk factors for VTE and hemorrhage. Finally, all patients were contacted by telephone after 3 months and asked whether any study outcome had occurred, i.e., if they had undergone examination for a suspected VTE, whether any hospital visits had taken place and whether they had adhered to

the assigned treatment. In case of no response, patients' general practitioners were contacted to determine if any study outcome or death had occurred. For all unresponsive patients the vital status was acquired from the Dutch population register. Detailed information on study outcomes was collected from patients' electronic hospital files and radiology reports. Data were centrally collected in a web-based database management system.[9]

Randomization and blinding

Eligible patients were randomly allocated to the study arms in a 1:1 ratio. Randomization was carried out centrally (online using Promise[9]) by the treating physician. To ensure concealment of treatment allocation the treating physicians were unaware of the allocation scheme and block sizes. Randomization was stratified by study center and by conservative or operative treatment (which was assessed at randomization). Patients and caregivers were not blinded for the allocated treatment.

Study outcomes

The primary outcome was the occurrence of symptomatic venous thromboembolism, i.e. deep vein thrombosis, or pulmonary embolism. The primary safety outcome was the incidence of major bleeding within the same time period.[10] Clinically relevant non-major bleeds (CRNMB) were considered as a secondary outcome (related to contact with a physician) and all other bleeds were registered as minor. All possible outcomes were evaluated and assessed by a blinded and independent outcome adjudication committee. All outcome definitions can be found in the Supplementary Appendix.

Sample size

We assumed an incidence of VTE in the absence of treatment of 2% as the basis of our sample size calculations. Based on a risk reduction of 85%[11], we calculated a necessary sample size of 625 subjects in each arm (alpha 0.05, power 80%, two-sided). To account for a maximum drop-out rate of 15%, we aimed to include 750 patients in each study arm. For our primary safety outcome, we assumed a risk of major bleeding of 0.3% which allowed us to determine an upper limit of the 95%CI of about 1%.[1,12,13]

Safety monitoring

A pre-specified interim analysis for safety purposes was planned and reviewed by an independent data safety monitoring board (DSMB) after 50% and 75% of the targeted

number of patients were included. If at interim analysis the intervention would prove to be clearly contraindicated by means of an increased risk of major bleeding (upper limit of the 95%Confidence Interval (CI) >1%), we considered to terminate the study prematurely. Furthermore, the DSMB provided advice on the conduct of the trial to the steering committee.

Statistical analysis

All analyses followed the pre-specified plan as described in the study protocol. Baseline characteristics were summarized as means with standard deviations (SD) or proportions as appropriate. Data on outcome events were analyzed by the intention-to-treat principle, excluding patients who were inadvertently randomized since they had not met in-or exclusion criteria. For the primary outcome, cumulative incidences with 95% Confidence Intervals (CI), based on the binomial distribution in both groups for symptomatic VTE were estimated and compared by means of relative risks (RR) and risk differences (RD) with their 95%CIs. Similar analyses were performed for the safety outcomes. In a per-protocol analysis we included only those individuals who had adhered to the study protocol. Analyses were performed in IBM SPSS Statistics for Windows, version 23 and in Stata, version 14 SE.

Results

Study population

From March 2012 through January 2016, 1519 patients were enrolled at eight study centers (Figure 1). 761 were randomly assigned to LMWH and 758 patients to no treatment. After randomization, 33 patients were excluded because the original in- or exclusion criteria had not been met (e.g. VTE in patient history, no cast); 14 in the LMWH group versus 19 in the no treatment group. Of the remaining patients a total of 23 withdrew consent and 28 were lost to follow-up, leading to 719 patients in the LMWH and 716 in the no treatment group who were included in the intention-to-treat analysis. Patient characteristics were well balanced across both groups. Overall, 49.9% of patients were men and mean age was 46.5 (SD16.5) years (Table 1). The majority of patients (1279, 89%) were treated with cast immobilization because of a fracture (Table 2). Among all patients with a fracture, 530 (41%) had one or more broken metatarsal bones and 492 (38%) had an ankle fracture. Surgery was performed in 170 patients as part of their treatment and 105 patients had multiple fractures.

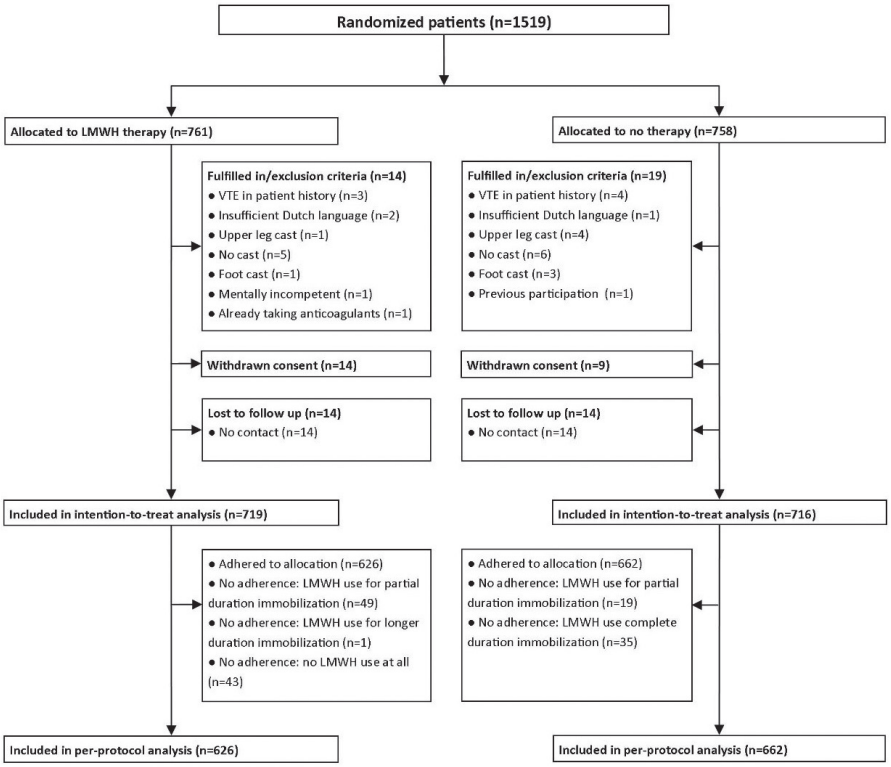

Figure 1. *Flow chart of patients*

Figure legend: Flow chart of patients enrolled, randomized and included in the intention to treat and per-protocol analysis.

Table 1. *Characteristics of study population*

Patient characteristics §	**LMWH* (n=719)**	**No treatment (n=716)**
Male sex, n (%)	347 (48.3)	369 (51.5)
Mean age, years	46.5±16.5	45.6±16.4
Mean BMI, kg/m^2 †	26.0±4.4	25.7±4.4
Smoking, n (%)		
Current	173 (26.1)	178 (26.8)
Ever	188 (28.4)	178 (24.9)
Oral contraceptives use, n (% of women)	86 (24.7)	69 (21.2)
Paid employment (%)	442 (66.6)	469 (65.5)
Cancer		
Within last year	8 (1.2)	9 (1.3)
More than 1 year ago	26 (3.9)	20 (3.0)
Family history of venous thromboembolism, n (%)	60 (10.6)	52 (9.4)

§ Percentages of complete data, data were missing for the following characteristics: BMI in 112 patients, Smoking in 107 patients, Oral contraceptives use in 45 patients, Paid employment in 102 patients, Cancer in 87 patients, Family history of venous thromboembolism 316 patients.

** Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

† BMI: body mass index in kilogram divided by the square of the height in meters.

Table 2. *Lower leg cast details*

Lower leg cast details §¶	**LMWH* (n=719)**	**No treatment (n=716)**
Duration cast in weeks, mean (SD)	4.9 (2.5)	4.9 (2.5)
Lower leg cast indication, n (%)		
Fracture	648 (90.1)	631 (88.1)
Achilles tendon rupture	40 (5.6)	54 (7.5)
Ankle distortion	18 (2.5)	17 (2.4)
Antalgic	6 (0.8)	3 (0.4)
Contusion	5 (0.7)	8 (1.1)
Other	2 (0.3)	3 (0.4)

Table 2. *Lower leg cast details (continued)*

Lower leg cast details §¶	**LMWH* (n=719)**	**No treatment (n=716)**
Fracture type, n(%)		
Ankle	253 (39.0)	239 (37.9)
44-A type	60 (28.3)	44 (22.1)
44-B type	125 (57.5)	129 (64.8)
44-C type	27 (12.7)	26 (13.1)
Other†	16 (7.5)	15 (7.5)
Metatarsal	276 (42.6)	254 (40.3)
Calcaneus	31 (4.8)	25 (4.0)
Pilon tibial	2 (0.3)	1 (0.2)
Tibia and fibula shaft	1 (0.2)	2 (0.3)
Talus	21 (3.2)	29 (4.6)
Tarsal	42 (6.5)	56 (8.9)
Phalanx	11 (1.7)	12 (1.9)
Lisfranc	4 (0.6)	2 (0.3)
Maisonneuve	2 (0.3)	3 (0.5)
Other	5 (0.8)	8 (1.3)
Multiple fractures, n (%)	53 (8.4)	52 (8.4)
Surgery, n (%)	91 (12.7)	79 (11.0)
Total duration operation in minutes, mean (SD)	75.2 (32.2)	78.5 (27.4)
Duration surgery in minutes, mean (SD)	50.2 (28.2)	50.9 (21.7)

§ Percentages of complete date, data were missing for the following characteristics: AO classification ankle fracture type in 50 patients, duration operation or surgery in 33 patients

¶ SD denotes Standard Deviation

** Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

† Fractures not meeting criteria to be classified in either type.

Effectiveness

In the LMWH group, 10/719 patients developed a VTE (6 DVTs, 3 PEs and 1 patient had both) for a cumulative incidence of 1.4% (95%CI 0.7 to 2.5) (Table 3). In the no treatment group, 13/716 developed a VTE (8 DVTs, 4 PEs and 1 patient developed both), for a cumulative incidence of 1.8% (95%CI 1.0 to 3.1). The RR for VTE following lower leg cast with LMWH therapy versus no treatment was 0.8 (95%CI 0.3 to 1.7) with a RD of -0.4% (95%CI -1.7 to 0.9). Additionally, one patient in each group developed a distal superficial vein thrombosis (which was not considered as an outcome event). The Supplementary Appendix shows all DVT and PE locations.

The study protocol was followed by 626/719 (87%) patients in the LMWH group and by 662/716 (92%) in the no treatment group (Figure 1). A VTE occurred in 10/626 patients in the LMWH group and in 12/662 patients in the no treatment group following a per-protocol analysis (Table 4). The cumulative incidence for VTE was 1.6% versus 1.8%, respectively, for an RR of 0.9 (95%CI 0.4 to 2.0). The 13th patient who developed VTE (assigned to no treatment), had used Nadroparin for 4 weeks after surgery (on this patient's own initiative).

Table 3. *Primary efficacy outcomes, Intention-to-treat analysis†*

Outcome	LMWH*(n=719), no. (%; 95%CI)	No treatment (n=716), no. (%; 95%CI)	RR (95%CI)	RD (95%CI), percentage points
Primary efficacy outcome				
DVT	6 (0.8; 0.3 to 1.8)	8 (1.1; 0.5 to 2.2)	0.7 (0.3 to 2.1)	-0.3 (-1.3 to 0.7)
PE	3 (0.4; 0.1 to 1.2)	4 (0.6; 0.2 to 1.4)	0.7 (0.2 to 3.3)	-0.1 (-0.9 to 0.6)
DVT and PE	1 (0.1; 0.0 to 0.8)	1 (0.1; 0.0 to 0.8)	1.0 (0.1 to 15.9)	0.0 (-0.4 to 0.4)
Total	10 (1.4; 0.7 to 2.5)	13 (1.8; 1.0 to 3.1)	0.8 (0.3 to 1.7)	-0.4 (-1.7 to 0.9)
Primary safety outcome				
Major Bleed	0 (0; 0 to 0.5)	0 (0; 0 to 0.5)	-	-
Secondary safety outcome				
CLNMB Bleed	1 (0.1; 0.0 to 0.8)	0 (0; 0 to 0.5)	-	0.1 (-0.1 to 0.4)

** Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

† DVT denotes Deep Vein Thrombosis, PE denotes Pulmonary Embolism, CI denotes Confidence Interval, RR denotes Relative Risk, RD denotes Risk Difference, CLNMB, denotes clinically relevant non-major bleeding

Table 4. *Primary efficacy outcomes, Per-protocol analysis†*

Outcome	LMWH*(n=626), n (%; 95%CI)	No treatment (n=662), n (%; 95%CI)	RR (95%CI)	RD (95%CI), percentage points
Primary efficacy outcome				
DVT	6 (1.0; 0.4 to 2.1)	7 (1.1; 0.4 to 2.2)	0.9 (0.3 to 2.7)	-0.1 (-1.2 to 1.0)
PE	3 (0.5; 0.1 to 1.4)	4 (0.6; 0.2 to 1.5)	0.8 (0.2 to 3.5)	-0.1 (-0.9 to 0.7)
DVT and PE	1 (0.2; 0.0 to 0.9)	1 (0.2; 0.0 to 0.8)	1.1 (0.1 to 16.9)	-0.0 (-0.4 to 0.4)
Total	10 (1.6; 0.8 to 2.9)	12 (1.8; 0.9 to 3.1)	0.9 (0.4 to 2.0)	-0.2 (-1.6 to 1.2)
Primary safety outcome				
Major Bleed	0 (0; 0 to 0.6)	0 (0; 0 to 0.6)	-	-
Secondary safety outcome				
CLNMB Bleed	1 (0.1; 0.0 to 0.9)	0 (0; 0 to 0.6)	-	0.2 (-0.2 to 0.5)

† DVT denotes Deep Vein Thrombosis, PE denotes Pulmonary Embolism, CI denotes Confidence Interval, RR denotes Relative Risk, RD denotes Risk Difference, CLNMB, denotes clinically relevant non-major bleeding

** Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

Safety outcome

During the 3-month follow-up period one CRNMB occurred in 1/719 (0.14%) patients in the LMWH group as compared with none in the no treatment group, while no major bleedings occurred. A minor bleeding was found in 56/719 (7.8%) and in 49/716 (6.8%) patients in the LMWH and no treatment group, respectively (Supplementary appendix). One patient assigned to no therapy died within 3 months after randomization, which death was assessed by the outcome adjudication committee as possibly due to pulmonary embolism. However, because no autopsy was performed and the patient was aged >90 years and suffered from heart failure, a conclusive diagnosis could not be made. The Supplementary appendix provides a sensitivity analysis including this possible event in the intention-to-treat analysis, which did not essentially change the main result. No deaths occurred among any of the patients who were lost to follow up.

Discussion

In the POT-CAST trial we investigated the effectiveness of thromboprophylaxis versus no treatment for the prevention of VTE in patients with lower leg cast immobilization. We found that treatment with anticoagulants during the complete period of cast immobilization was not effective for the prevention of VTE.

Previous findings from six small trials (totaling 1536 patients) are in contrast with ours with a pooled odds ratio of 0.49 (95%CI 0.34-0.72) and 0.16 (95%CI 0.05 to 0.56) (only in four trials) in favor of LMWH treatment for the prevention of asymptomatic (DVT only) and symptomatic VTE, respectively.[6] Nevertheless, in addition to not being individually powered for symptomatic events, these trials suffered from severe methodological weaknesses, such as an overall loss to follow up of 32%.[2] Furthermore, most trials included only patients with high risk for VTE, e.g., only patients undergoing surgery[4] or only patients with a duration of cast immobilization of more than five weeks.[5] For these reasons, the ACCP guidelines currently refrain from advising in favor of thromboprophylaxis in patients with lower leg cast immobilization.[7]

Strengths of the POT-CAST trial are first the pragmatic design: participants formed a nonselected, wide variety of patients in need of lower leg cast immobilization, and no restrictions were made regarding cast duration (apart from an expected treatment of at least one week). The exclusion criteria were minimal, hence maximizing generalizability towards the clinic. Also, although the study design was open, a blinded outcome adjudication committee classified all events. Finally, we had almost no loss to follow-up (2%) and only a limited number of patients withdrew consent (1%).

Potential limitations that may explain the minimal effect are first the open design which theoretically could have led to differential contacting of a physician in case of signs and symptoms of VTE, which may have occurred as VTE was suspected 17 vs 25 times in the LMWH and no treatment group, respectively. Nevertheless, the diagnosis was confirmed at the same rate in both groups, so even though the suspicion rate may have differed, this did not lead to bias: 10 (59%) vs 13 (52%) patients in the LMWH and no treatment group, respectively. It should be noted that we intentionally chose for non-blinding to reflect general practice, where in 'real life' patients may also contact their doctor differently depending on their type of treatment. Second, treatment adherence was not 100%, though good (and monitored three times during three months); 87%

of patients allocated to LMWH adhered to this treatment as compared with 92% in the group allocated to no treatment. Furthermore, out of the 93 patients who did not adhere to LMWH, 49 adhered at least partially (prophylactic treatment was most often stopped because patients were mobile or changed to a less rigid cast, e.g. foot cast). Again, these figures represent daily life situations and it is not to be expected adherence would be better outside a trial context (a previous large prospective study in 4388 orthopedic surgery patients showed an identical adherence rate of 87%)[14] Moreover, the per protocol analyses showed similar results as the intention-to-treat analysis. Lastly, the absence of effect may have been due to the duration, dose, or type of anticoagulant treatment. For example, 9/23 patients developed VTE after their cast was removed, of whom 6 had been treated with LMWH. This might indicate a need for extended prophylactic treatment, possibly in high-risk groups only: It can be hypothesized that patients who develop symptomatic VTE under treatment have a high baseline risk, where cast application is a relatively small trigger, added to the baseline risk and leading to thrombosis.[15] In such individuals their high risk cannot be sufficiently lowered with a prophylactic dose of anticoagulant treatment. We demonstrated in another dataset that patients who developed VTE after plaster cast immobilization were found to have (several) other risk factors for VTE.[8] In the current trial, other risk factors were indeed present in the patients who developed VTE under treatment, e.g. high age, male sex, hormone use, family history of VTE. A similar situation is possibly present in patients with hip replacement where 2% of patients still develop VTE despite anticoagulant prophylaxis.[16] We therefore speculate that for these 'doomed' individuals the routine prophylactic dose is not sufficient. Nevertheless, exposing all patients with plaster cast to a more intense anticoagulant scheme is not feasible considering the numbers needed to treat and harm. Risk prediction, identification of high-risk groups (which we previously showed to be feasible[17]) and targeted treatment should therefore be the topic for further research in this patient group.

In conclusion, in the POT-CAST trial we found that for patients requiring lower leg cast immobilization, anticoagulant medication was not superior to no therapy for the prevention of symptomatic VTE. In addition, no critical safety issues regarding treatment were found, leading to an overall neutral risk-benefit ratio for anticoagulant therapy. Clinicians should not routinely prescribe thromboprophylaxis in patients treated with lower leg cast immobilization.

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Supplementary appendix

Participating study centers (all located in the Netherlands)

Alrijne Hospital, Leiderdorp
Groene Hart Hospital, Gouda
Haga Hospital, The Hague
Isala Hospital, Zwolle
Medical Center Haaglanden Hospital, The Hague
Leiden University Medical Center, Leiden
Reinier de Graaf Hospital, Delft

Primary and Secondary Outcome definitions

Primary study outcomes

The primary efficacy outcome is symptomatic venous thrombosis, i.e., deep venous thrombosis (DVT) or fatal or non-fatal pulmonary embolism (PE).

The following definitions are applied to confirm a suspected episode of symptomatic PE/DVT:

1. DVT: abnormal compression ultrasound
2. PE: an intraluminal filling defect in segmental or more proximal branches on spiral CT scan or a perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan or detected at autopsy.

The primary safety outcome is major bleeding, defined according to the guidelines of the ISTH[1]:

a) fatal bleeding, or
b) symptomatic bleeding in a critical area or organ, or
c) extra surgical site bleeding causing a fall in hemoglobin level of 1.24 mmol/L (2.0 g/dl) or more, or leading to transfusion of one or more units of whole blood or red cells, or
d) surgical site bleeding that requires a second intervention or a hemarthrosis interfering with rehabilitation, or surgical site bleeding that needs blood transfusion.

Secondary study outcomes

Other clinically relevant bleeding, defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, (temporary) cessation of study treatment, or associated with discomfort such as pain, or impairment of activities of daily life.

[1] Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010;8(1):202-204.

***Table** - Location of thrombotic event*

Location thrombotic event	LMWH Total no.	No Treatment Total no.	Total no.
Pulmonary embolism*			
Peripheral	1	1	2
Central	0	1	1
Multiple	3	3	6
Deep vein thrombosis*			
Proximal	5	3	8
Distal	2	6	8

**Two patients had both deep vein thrombosis and pulmonary embolism*

Table. *List of bleeding events*

Bleeding type	**LMWH Total no.**	**No therapy Total no.**
Major bleeding †	0	0
Total	**0**	**0**
Clinically relevant bleeding ‡		
Hematuria	1	0
Total	**1**	**0**
Minor bleeding §		
Rectal bleeding	1	2
Menstruation (heavier than normal)	1	0
Throat	1	0
Abdomen (skin)	1	0
Arms, legs	2	2
Nose bleeding §	33	27
Hematoma >3cm §	17	18
Spontaneous hematoma >3cm*	9	11
Hematoma on other place than arms or legs >3cm*	8	2
Grand Total ¶	**56**	**49**

† *defined according to the ISTH guidelines (JTH 2010;8:202-4)*

‡ *defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, (temporary) cessation of study treatment, or associated with discomfort such as pain, or impairment of activities of daily life.*

§ *defined as other bleeding not meeting the criteria for major or clinically relevant bleeding, no contact with a physician.*

**does not add up as patients could have both conditions.*

¶ *total minor bleedings (minor bleeding and nose bleeding and hematoma>3cm)*

Sensitivity analysis

One patient assigned to no treatment died within 3 months after randomization, which death was assessed by the outcome adjudication committee as possibly due to pulmonary embolism. However, because no autopsy was performed and the patient was aged >90 years and suffered from heart failure, a conclusive diagnosis could not be drawn. This possible pulmonary embolism is added to the analysis shown below. The main results did not show an essential change (RR 0.7, 95%CI 0.3 to 1.6).

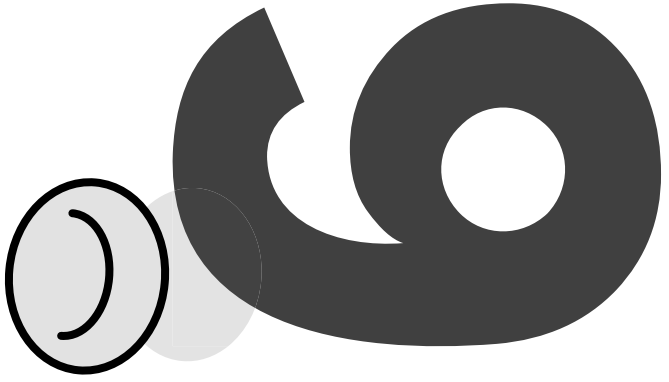
Table. *Sensitivity analysis – changes indicated in bold*

Outcome†	**LMWH*(n=719), no. (%; 95%CI)**	**No treatment (n=716), no. (%; 95%CI)**	**RR (95%CI)**	**RD (95%CI), percentage points**
Primary efficacy outcome				
DVT	6 (0.8; 0.3 to 1.8)	8 (1.1; 0.5 to 2.2)		-0.3 (-1.5 to 0.8)
PE	3 (0.4; 010 to 1.2)	**5 (0.7; 0.2 to 1.6)**		-0.3 (-1.3 to 0.6)
DVT and PE	1 (0.1; 0.0 to 0.8)	1 (0.1; 0.0 to 0.8)		0.0 (-0.7 to 0.7)
Total	10 (1.4; 0.7 to 2.5)	**14 (2.0; 1.1 to 3.3)**	**0.7 (0.3 to 1.6)**	**-0.6 (-1.9 to 0.8)**
Primary safety outcome				
Major Bleeding	0 (0; 0 to 0.5)	0 (0; 0 to 0.5)	-	0.0 (-0.5 to 0.5)
Secondary safety outcome				
CLNMB Bleeding ‡	1 (0.1; 0.0 to 0.8)	0 (0; 0 to 0.5)	-	0.1 (-0.4 to 0.8)

† *DVT denotes deep vein thrombosis, PE denotes Pulmonary Embolism, CI denotes Confidence Interval, RR denotes Relative Risk, RD denotes Risk Difference*

***** *Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

‡ *CLNMB: clinically relevant non-major bleeding*



CHAPTER

Prevention of venous thromboembolism after knee arthroscopy: a randomized controlled trial

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Abstract

Background

The effectiveness of thromboprophylaxis for the prevention of venous thromboembolism (VTE) after knee arthroscopy is disputed. We contrasted anticoagulant therapy with no therapy for the prevention of symptomatic VTE following knee arthroscopy.

Methods

We conducted a pragmatic, multicenter, randomized, controlled, open label, blinded end-point trial in which patients were assigned to receive either low-molecular-weight-heparin (LMWH), 2850 IU (or 5700 IU in patients >100 kilograms) once daily, for 8 days post-operatively, or no therapy. The primary outcome was the occurrence of symptomatic VTE within three months following knee arthroscopy and the primary safety outcome was the occurrence of major bleeding in the same time period.

Results

6413 patients were screened for eligibility of whom 1543 were included in the study and 1451 analyzed in the intention-to-treat analysis. A venous thromboembolic event occurred in 5/731 (0.7%) patients assigned to LMWH and in 3/720 (0.4%) patients assigned to no therapy, for a relative risk (RR) with LMWH of 1.6; 95% confidence interval [CI] 0.4 to 6.8; (risk difference 0.3%; 95% CI -0.5 to 1.0). A major bleeding occurred in 1/731 (0.1%) patients in the LMWH and in 1/720 (0.1%) patients in the no-treatment group (RR 1.0; 95%CI [0.1 to 15.7]).

Conclusions

The POT-KAST trial showed that a prophylactic regimen of LMWH therapy for eight days was not effective for the prevention of symptomatic VTE in patients undergoing knee arthroscopy, which risk appeared to be low. These results do not support routine thromboprophylaxis in patients after knee arthroscopy.

Introduction

Patients who undergo arthroscopic knee surgery are at increased risk of developing venous thromboembolism (VTE) (i.e. deep vein thrombosis [DVT] or pulmonary embolism [PE]).[1] Venous thromboembolism is an important health-care problem, with considerable mortality, morbidity and resource expenditure.[2-4] For most orthopedic interventions, thrombosis prophylaxis with anticoagulant medication is well established, as it strongly reduces the risk of thrombosis, while the risk of bleeding is only slightly increased.[5-7] However, for arthroscopic knee surgery it is uncertain whether thrombosis prophylaxis is effective, despite it being the most commonly performed orthopedic procedure worldwide, with an estimated >4 million knee arthroscopies each year. [6,8]

To answer this question, six randomized controlled trials have previously been performed in these patients comparing anticoagulant treatment with no therapy.[9-11] However, these trials have not settled the question, since they used asymptomatic thrombosis as the primary outcome, generally chosen to reduce the required sample size. These trials were therefore underpowered to reach definite conclusions on the prevention of symptomatic events. Moreover, with the small sample sizes, side effects of the treatment were low in number and an overall risk-benefit balance could not be established. Due to this lack of evidence, international guidelines have been reluctant to advise in favor of or against anticoagulant treatment in these patients.[6,7]

The Prevention Of Thrombosis after Knee ArthroScopy Trial [POT-KAST] was designed to compare anticoagulant treatment (Low-Molecular-Weight-Heparin [LWMH]) with no therapy for the prevention of symptomatic VTE in patients who underwent arthroscopic knee surgery. We hypothesized that treatment with anticoagulants for 8 days post-operatively would be effective for the prevention of symptomatic VTE and that this benefit outweighed the bleeding risk.

Methods

Study oversight and design

The POT-KAST trial is a prospective, multicenter, randomized, controlled, open label, blinded endpoint trial comparing two treatment strategies, i.e., one by which the anticoagulant LMWH is administered versus one by which it is not, in patients who undergo knee arthroscopy. The POT-KAST study had a pragmatic design to maximize generalizability. The trial protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center; no methodological changes were made after approval. The trial was funded by The Netherlands Organization for Health Research and Development (project number 171102001) which had no role in the study design, analysis or preparation of the manuscript. The trial was registered at clinicaltrials.gov, number: NCT01542723. All authors of the study group vouch for the accuracy and completeness of the reported data.

Participants

The trial was performed in eight hospitals in the Netherlands (six teaching hospitals and two private medical care orthopedic focus clinics, Supplementary Appendix). All patients, aged 18 years or older, scheduled for knee arthroscopy for one of the following indications: meniscectomy, diagnostic arthroscopy or removal of loose bodies were eligible for inclusion. Exclusion criteria were a history of VTE, contra-indications to use of LMWH (e.g. previous allergic reaction), pregnancy and current use of anticoagulant therapy for other indications (either LMWH, vitamin K antagonists or direct oral anticoagulants). Furthermore, patients with insufficient knowledge of the Dutch language, mental or physical disability to fulfill study requirements and patients who had previously participated in the trial were not included. All participants provided written informed consent.

Study procedures and intervention

Eligible patients were randomly assigned to receive a prophylactic dosage of LMWH (type of LMWH according to the hospitals preference) once daily for 8 days post-operatively versus no treatment. The first dose was administered post-operatively on the day of surgery before discharge on the same day. Nadroparin 2850 IU subcutaneous or dalteparin 2500 IU subcutaneous was used for patients weighing less than 100kg, whereas patients over 100kg received a double dose.

Patients received an information leaflet for signs and symptoms of VTE and were advised to seek medical care if such symptoms arose. Follow-up started from the day of the procedure and the total duration was 3 months as after this period the risk is back to baseline.1 Digital (online) or postal questionnaires on study outcomes, study compliance and on study medication adherence were sent 2 and 6 weeks after start of follow-up. Additionally, all patients were contacted by telephone after 3 months and asked whether any study outcome had occurred, i.e., if they had undergone examination for a suspected VTE, whether any hospital visits had taken place and whether they had adhered to the assigned treatment. The patients were also requested to complete a questionnaire on risk factors for VTE and hemorrhage. In case of no response, patients' general practitioners were contacted to determine if any study outcome or death had occurred. For all unresponsive patients the vital status was acquired from the Dutch population register. Detailed information on study outcomes was collected from patients' electronic hospital files and radiology reports. Data were centrally collected in an online database management system.[9]

Randomization and blinding

Eligible patients were randomly allocated to the study arms in a 1:1 ratio. Block randomization with variable block sizes was used. The randomization was performed centrally (using Promise) by the data-management of the study.[9] To ensure concealment of treatment allocation the data management and researchers were unaware of the allocation scheme and block sizes. Randomization was stratified according to study center. Patients and caregivers were not blinded for the allocated treatment.

Study outcomes

The primary outcome was the occurrence of symptomatic venous thromboembolism, i.e. deep vein thrombosis, or pulmonary embolism. The primary safety outcome was the incidence of major bleeding.[10] Other clinically relevant non major bleeds (CRNMB) were considered as a secondary outcome (related to contact with a physician) and all other bleeds were registered as minor. All possible outcomes were evaluated and assessed by a blinded and independent outcome adjudication committee. All outcome definitions can be found in the Supplementary Appendix.

Sample size

We assumed an incidence of symptomatic VTE in the absence of treatment of 2% as the basis of our sample size calculations.[11,12] Based on a risk reduction of 85%[11], we calculated a sample size of 625 subjects in each arm (alpha 0.05, power 80%, two sided). To account for a maximum drop-out rate of 15%, we aimed to include 750 patients in each study arm. For our primary safety outcome, we assumed a risk of major bleeding of 0.3% which allowed us to determine an upper limit of the 95%CI of about 1%.[13-15]

Safety monitoring

A pre-specified interim analysis for safety purposes was planned and reviewed by an independent data safety monitoring board (DSMB) when 50% and 75% of the target number of patients was included. If at interim analysis the intervention would prove to be clearly contraindicated by means of an increased risk of major bleeding (upper limit of the 95%CI >1%), we considered to terminate the study prematurely.

Statistical analysis

All analyses followed the pre-specified plan as described in the study protocol. Baseline characteristics were summarized as means with standard deviations (SD) or proportions as appropriate. Data on outcome events were analyzed by the intention-to-treat principle, excluding patients who were inadvertently randomized since they had not met in-or exclusion criteria. For the primary outcome, cumulative incidences with 95% Confidence Intervals (CI) based on the binomial distribution in both groups for symptomatic VTE were estimated and compared by means of relative risks (RR) and risk differences (RD) with their 95%CIs. Similar analyses were performed for the safety outcomes. In a per-protocol analysis we included only those individuals who had adhered to the study protocol. Analyses were performed in IBM SPSS Statistics for Windows, version 23 and in Stata, version 14 SE.

Results

Study population

From May 2012 to January 2016, 6413 patients were screened for eligibility of whom 1543 were included at eight centers in The Netherlands (Figure 1). Of these randomized patients, 773 were allocated to LMWH therapy and 770 to no therapy. In total 30 patients were excluded after randomization because the original in- or exclusion criteria

turned out not to have been met (e.g., surgery cancellation, n=14). Of the remaining participants, 37 withdrew consent and 25 could not be reached for occurrence of an outcome event (vital status available), leading to a total of 731 patients allocated to LMWH versus 720 to no treatment who were included in the intention-to-treat analysis. Baseline characteristics were similar between groups (Table 1). 55.8% of all participants were men and mean age was 48.5 (SD 12.5) years. Most patients were classified as American Society of Anesthesiologists Class I (61.1%) and about half received general anesthesia (Table 2). The majority of patients underwent a meniscectomy (1118, 77%), followed by diagnostic arthroscopy (114, 8%). 340 (23%) other procedures were performed (multiple interventions possible, see Supplementary Appendix).

Table 1. *Characteristics of study population*

Patient characteristics §	**LMWH treatment* (n=731)**	**No treatment (n=720)**
Male sex, n (%)	414 (56.6)	396 (55.0)
Mean age ±SD, years	48.1±12.8	49.1±12.3
Mean BMI, kg/m^2 †	27.1±3.9	26.8±4.0
ASA classification‡		
ASA 1, n (%)	438 (63.3)	449 (62.4)
ASA 2, n (%)	248 (35.8)	236 (32.8)
ASA 3, n (%)	6 (0.9)	4 (0.6)
Smoking, n (%)		
Current	131 (18.3)	140 (19.8)
Ever	247 (34.5)	244 (34.6)
Contraceptives use, n (% of women)¶	94 (30.5)	83 (25.9)
Paid employment (%)	559 (78.5)	534 (75.4)
Cancer		
Within last year	6 (0.8)	6 (0.8)
More than 1 year ago	27 (3.8)	23 (3.3)
Family history of VTE (1st degree), n (%)	82 (11.5)	87 (12.3)

***** *Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

† *BMI: body mass index in kg/m^2*

‡ *ASA classification: American Society of Anesthesiologists physical status classification system*

¶ *Any hormonal contraceptive us, e.g., oral contraceptives, intra-uterine devices.*

§ *Data were missing for the following characteristics: BMI in 28 patients, ASA Classification in 70 patients, Smoking in 29 patients, Oral contraceptives use in 13 patients, Paid employment in 31 patients, Cancer in 30 patients, Family history of VTE in 31 patients.*

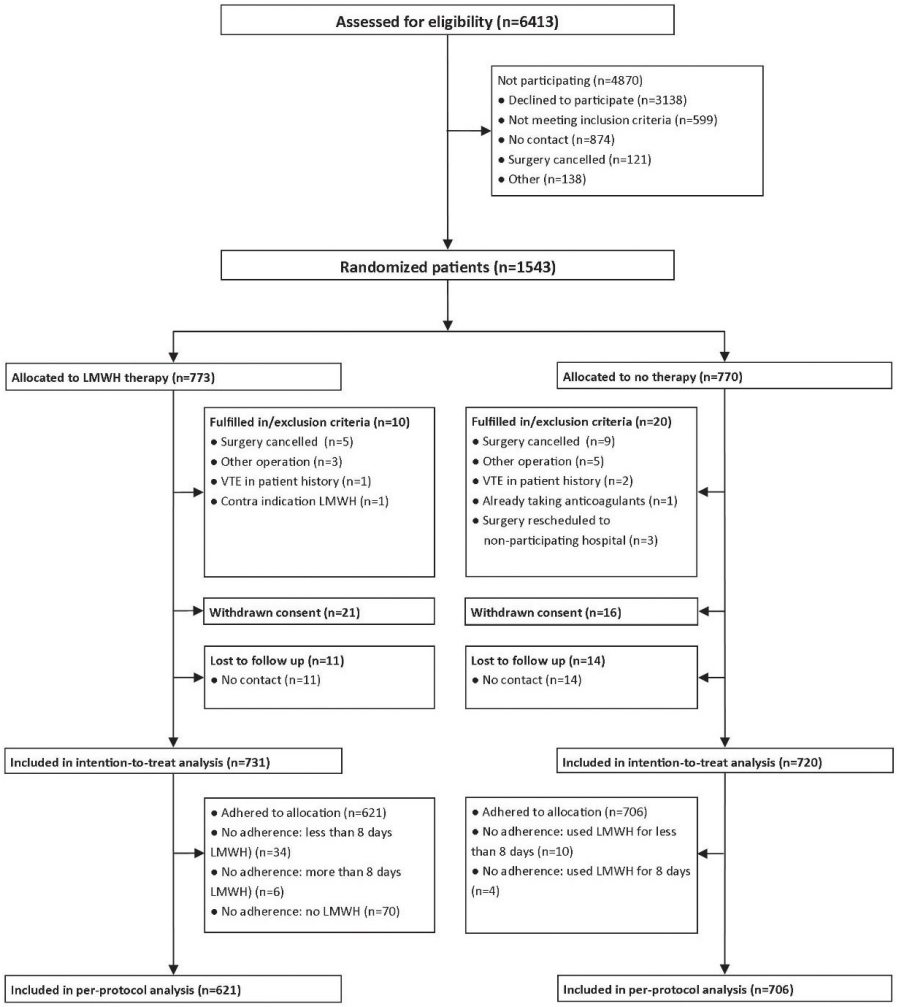

Figure 1. *Flow chart of patients*

Figure legend: Flow chart of patients enrolled, randomized and included in the intention-to-treat and per-protocol analysis.

Table 2. *Surgery details*

Surgery details §	LMWH* (n=731)	No treatment (n=720)
Total duration operation in minutes, mean (SD)	26 (11)	26 (11)
Duration surgery in minutes, mean (SD)	16 (8)	15 (8)
Anesthesia:		
General, n(%)	362 (50.6)	345 (48.7)
Spinal, n(%)	353 (49.3)	363 (51.2)
Epidural	1 (0.1)	1 (0.1)
Procedure: †		
Meniscectomy, n (%)	562 (76.9)	556 (77.2)
Removal of loose bodies, n(%)	41 (5.6)	36 (5.0)
Diagnostic arthroscopy, n (%)	56 (7.7)	58 (8.1)
Other‡, n (%)	168 (23.0)	172 (23.9)
Tourniquet use, yes (%)	688 (97.9)	673 (97.8)

***** *Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

† *Does not add up to 100% as some patients had multiple interventions.*

‡ *Full list of other interventions listed in the Supplementary Appendix.*

§ *Data were missing for the following characteristics: Duration Operation and Surgery in 97 patients, Anesthesia in 26 patients, Tourniquet use in 60 patients.*

Effectiveness

Among patients randomized in the LMWH group, the primary outcome was suspected 12/731 times, out of which 4 DVTs and 1 PE were confirmed. In the no treatment group, 11/720 patients were investigated for VTE of whom 2 patients were diagnosed with DVT and 1 with PE. In the intention-to treat analysis, the cumulative incidence of VTE within 3 months was 0.7% (95%CI 0.2 to 1.6) in the LMWH and 0.4% (95%CI 0.1 to 1.2) in the no therapy group. This resulted in a RR for VTE of 1.6 (95%CI 0.4 to 6.8) for LMWH vs no treatment (RD 0.3%, 95%CI -0.5 to 1.0) (Table 3).

Table 3. *Primary outcomes, Intention-to-treat analysis†*

Outcome	LMWH* (n=731), n (%, 95%CI)	No treatment (n=720), n (%; 95%CI)	RR (95%CI)	RD (95%CI), percentage points
Primary outcome				
DVT	4 (0.5, 0.1 - 1.4)	2 (0.3, 0.0 - 1.0)	2.0 (0.4 - 10.7)	0.3 (-0.4 - 0.9)
PE	1 (0.1, 0.0 -0.8)	1 (0.1, 0.0 - 0.8)	1.0 (0.1 - 15.7)	0.0 (-0.4 - 0.4)
DVT and PE	0 (-)	0 (-)	-	-
Total	5 (0.7, 0.2 -1.6)	3 (0.4, 0.1 - 1.2)	1.6 (0.4 - 6.8)	0.3 (-0.5 - 1.0)
Primary safety outcome				
Major bleeding	1 (0.1, 0.0 - 0.8)	1 (0.1, 0.0 - 0.8)	1.0 (0.1 - 15.7)	0.0 (-0.4 - 0.4)
Secondary safety outcome				
Relevant minor bleeding	1 (0.1, 0.0 - 0.8)	3 (0.4, 0.1 - 1.2)	0.3 (0.0 - 3.1)	-0.3 (-0.8 - 0.3)

***** *Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

† DVT denotes Deep Vein Thrombosis, PE denotes Pulmonary Embolism, CI denotes Confidence Interval, RR denotes Relative Risk, RD denotes Risk Difference

In the per-protocol analysis, 621/731 (85%) patients allocated to LMWH followed the study protocol compared with 706/720 (98%) patients who were allocated to the no treatment group (Figure 1). Here, VTE was confirmed in 4/621 (0.6%) patients using LMWH as compared with 3/706 (0.4%) patients in the no therapy group (RR 1.5, 95%CI 0.3 to 6.7) (Table 4). The 8th VTE case, who was assigned to LMWH, did not take LMWH but a regimen of 80mg carbasalate calcium for one week instead.

Table 4. *Primary outcomes, per-protocol analysis†*

Outcome	LMWH*(n=621), n (%; 95%CI)	No treatment (n=706), n (%; 95%CI)	RR (95%CI)	RD (95%CI), percentage points
Primary efficacy outcome				
DVT	4 (0.6, 0.2 - 1.6)	2 (0.3, 0.0 - 1.0)	2.3 (0.4 - 12.4)	0.4 (-0.4 - 1.1)
PE	0 (-)	1 (0.1, 0.0 - 0.8)	∞	-0.1 (-0.4 - 0.1)
DVT and PE	0 (-)	0 (-)	-	-
Total	4 (0.6, 0.2 - 1.6)	3 (0.4, 0.1 - 1.2)	1.5 (0.3 - 6.7)	0.2 (-0.6 - 1.0)
Primary safety outcome				
Major bleeding	1 (0.2, 0.0 - 0.9)	1 (0.1, 0.0 - 0.8)	1.1 (0.1 - 18.1)	0.0 (-0.4 - 0.4)
Secondary safety outcome				
Minor bleeding	1 (0.2, 0.0 - 0.9)	3 (0.4, 0.1 - 1.2)	0.4 (0.0 - 3.6)	-0.3 (-0.8 - 0.3)

***** *Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

† *DVT denotes Deep Vein Thrombosis, PE denotes Pulmonary Embolism, CI denotes Confidence Interval, RR denotes Relative Risk, RD denotes Risk Difference*

Safety outcome

Two major bleedings occurred during the study (Table 3). One patient (1/731; 0.1%) assigned to LMWH developed a hemarthrosis (knee) and one patient assigned to no treatment (1/720; 0.1%) developed a surgical site bleeding two days post-operatively requiring re-intervention (RR 1.0, 95%CI 0.1 to 15.7). A CRNMB occurred in 1/731 (0.1%) patients and in 3/720 (0.4%) patients in the treated and non-treated group respectively (RR 0.3, 95%CI 0.0 - 3.1). Minor bleeding occurred in 71/731 (9.7%) and in 43/720 (6.0%) patients in the treated and non-treated group respectively (Supplementary Appendix). No patients died within the follow-up period (also confirmed for all patients who were lost to follow-up).

Discussion

We found no beneficial effect of thromboprophylaxis (8 days LMWH post-operatively) on the prevention of symptomatic VTE after knee arthroscopy. In both groups one major bleeding occurred, demonstrating an overall neutral risk-benefit ratio for treatment with LMWH in patients undergoing knee arthroscopy.

These results contradict previous findings from a meta-analysis on four small RCTs (included numbers: 36, 130, 122, 239) that suggested a beneficial effect on symptomatic VTE, with a pooled RR for LMWH vs no treatment of 0.42 (95%CI 0.06 – 3.14).[11] In a larger trial, where LMWH for 7 days was compared with use of compression stockings, including about 650 subjects in each arm, four symptomatic thrombotic events were detected in the LMWH group (0.6%) as compared with 14 in the control group (2.1%) [RR 0.3, 95%CI 0.1-0.9].[12] More recently, the same group compared rivaroxaban with placebo in 241 randomized patients and found incidences of 0.8% and 6.1% in the treated and untreated groups respectively.[16] However, in both trials all participants were subjected to ultrasonographic screening for VTE at which time questions were asked about possible signs and symptoms. This clearly does not reflect identification of VTE in general clinical practice, and has therefore led to overestimation of the incidences.[17] Due to the these limitations, the need for stronger evidence has been expressed in several reviews and guidelines.[6,11,18]

Strengths of the POT-KAST trial are the pragmatic design in which two treatment strategies were compared, with conditions set to approximate general clinical practice as much as possible. Furthermore, although this was an open label trial, a blinded outcome adjudication committee classified all events. Lastly, the completeness of follow-up was high (98%) and few patients withdrew consent (2%).

Limitations that may explain our negative findings are firstly limited power due to the incidence of symptomatic VTE that was lower than expected, i.e. 0.6%. This low incidence is in line with recent observational studies that reported a cumulative incidence of 0.3% (95%CI 0.3-0.5) for VTE within 3 months and 0.4% (95% CI, 0.2–0.5) within 6 weeks, where in both studies the vast majority of patients did not receive any form of anticoagulants.[19,20] Furthermore, a meta-analysis showed a pooled incidence for VTE of 0.6% (95%CI 0.3-1.1) in 571.793 arthroscopic meniscectomy procedures.[21] In contrast, in the randomized trials performed on this topic much higher incidences of 0.9% (95%CI

0.3-2.1) up to 5.3% (95%CI 2.4-11.0) have been reported, on which figures our samples size calculations have been based.[6,11,12] The lower risks from the more recent studies can possibly be attributed to introduction of fast-track mobilization programs directly after surgery instead of bedrest for a couple of days.[22,23] If we assume, based on our own data and that of the recent observational studies, that the true incidence is indeed close to 0.6%, such low incidence supports futility of prophylactic treatment with anticoagulants as the number needed to treat would be huge whatever the effect of anticoagulant therapy. Furthermore, in this situation the harms introduced by anticoagulant treatment will likely outweigh its benefits when we consider the incidence of minor bleedings (9.7% vs 6.0%) as well as the costs accompanying pharmacological treatment. A second possible explanation for our null result could be treatment compliance. Seventy patients (9.6%) allocated to LMWH did not use this therapy and 34 (4.7%) patients used LMWH for less than the full eight days. Yet, these figures represent daily practice situations,[24] which the study was designed to show (instead of pure drug efficacy). Moreover, the per-protocol analysis showed similar results as the intention-to-treat analysis. Another explanation for our findings might have been the nonblinded study design. For example, patients not randomized to LMWH could have contacted their physician earlier in case of signs and symptoms of VTE. However, a VTE was suspected at the same rate in both groups. Besides, non-blinding again reflects the general practice situation, where in 'real life' patients may also contact their doctor differently depending on their type of treatment. Lastly, the lack of effect may have been due to dosage, duration or type of anticoagulant treatment: the prophylactic dose of 2850 I.E. might have been too low, despite it being the standard dose for thromboprophylaxis. Raising this dosage implies a higher bleeding risk, thereby resulting in a lower number needed to harm, which would outweigh the number needed to treat. All events occurred after the treatment period of eight days. This might indicate a need for longer treatment, although this was opposed in an earlier trial that reported an increased bleeding risk and no additional benefit for 14 versus 7 days of treatment.[12] Finally, it may be argued that use of a Direct Oral Anticoagulant (DOAC) would have led to different results. A recent meta-analysis including 5 randomized trials where DOACs were compared with LMWH in patients who received thrombosis prophylaxis after hip or knee surgery showed no difference in efficacy, which makes it unlikely that DOAC use would have led to different conclusions in our study.[25] Furthermore, even if DOACs would be effective, the number needed to treat would still be too large to justify this treatment in all patients. A final possible limitation is that patients who declined to participate could have been different with

respect to thrombosis risk from those who did participate. However, they were of similar age and sex as included patients, indicating no major differences.

Currently, the ACCP guidelines cautiously suggest no thromboprophylaxis in patients undergoing knee arthroscopy without a history of VTE and that screening for asymptomatic VTE should be avoided. We agree that this guideline should be followed in all patients without a history of VTE. In an earlier study we demonstrated that in patients who develop VTE after knee arthroscopy, several other risk factors for VTE were present.[1] We therefore believe there might be an indication for identifying high risk patients to tailor individualized thromboprophylactic strategies. For those patients at high risk for VTE, higher dosage and/or longer treatment might be warranted, while in all others treatment can be safely withheld. This should obviously be the topic of further study.

In conclusion, a prophylactic regimen of LMWH therapy for eight days is not effective for the prevention of VTE in patients undergoing knee arthroscopy. Clinicians should not routinely prescribe thromboprophylaxis in these patients.

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Supplementary appendix

Participating study centers (all located in the Netherlands)

Alrijne Hospital, Leiderdorp
Groene Hart Hospital, Gouda
Haga Hospital, The Hague
Isala Hospital, Zwolle
Medical Center Haaglanden Hospital, The Hague
Orthopedium Clinic, Delft
Park Medical Center, Rotterdam
Reinier de Graaf Hospital, Delft

Primary and Secondary Outcome definitions

Primary study outcomes

The primary efficacy outcome is symptomatic venous thrombosis, i.e., deep venous thrombosis (DVT) or fatal or non-fatal pulmonary embolism (PE).

The following definitions are applied to confirm a suspected episode of symptomatic PE/DVT:

1. DVT: abnormal compression ultrasound
2. PE: an intraluminal filling defect in segmental or more proximal branches on spiral CT scan or a perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan or detected at autopsy.

The primary safety outcome is major bleeding, defined according to the guidelines of the ISTH[1]:

a) fatal bleeding, or
b) symptomatic bleeding in a critical area or organ, or
c) extra surgical site bleeding causing a fall in hemoglobin level of 1.24 mmol/L (2.0 g/dl) or more, or leading to transfusion of one or more units of whole blood or red cells, or
d) surgical site bleeding that requires a second intervention or a hemarthrosis interfering with rehabilitation, or surgical site bleeding that needs blood transfusion.

Secondary study outcomes

Other clinically relevant bleeding, defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, (temporary) cessation of study treatment, or associated with discomfort such as pain, or impairment of activities of daily life.

[1] Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010;8(1):202-204.

Table. *Full list of other interventions during knee arthroscopy*

Interventions*	**Total no.**
Debridement (e.g. shaving cartilage, scar tissue)	180
Meniscal suture	24
Micro fracturing, drilling	19
Excision cyclops lesion	32
Partial synovectomy	22
Debridement synovitis	9
Needling meniscus	1
Biopsy	2
Knee arthroscopy both knees	1
Resection Cyst	21
Simple arthrotomy	2
Split or resection plica	21
Other	6

**Some patients had multiple interventions during surgery*

Table. *POT-KAST - Location of thrombotic event*

Study center	LMWH Total no.	No treatment Total no.	Total no.
Pulmonary Embolism			
Peripheral			
Central			
Multiple	1	1	2
Deep Vein Thrombosis			
Proximal	2	2	4
Distal	2		2

Table. *POT-KAST - List of bleedings events*

Bleeding type	LMWH Total no.	No therapy Total no.
Major bleeding †		
Surgical site bleeding, 2 days post-operative needing re-intervention		1
Hemarthrosis operated knee	1	
Total	1	1
Clinically relevant bleeding ‡		
Hematoma knee after fall on knee		1
Hematoma knee		2
Rectal bleeding	1	
Total	1	3

Table. *POT-KAST - List of bleedings events (continued)*

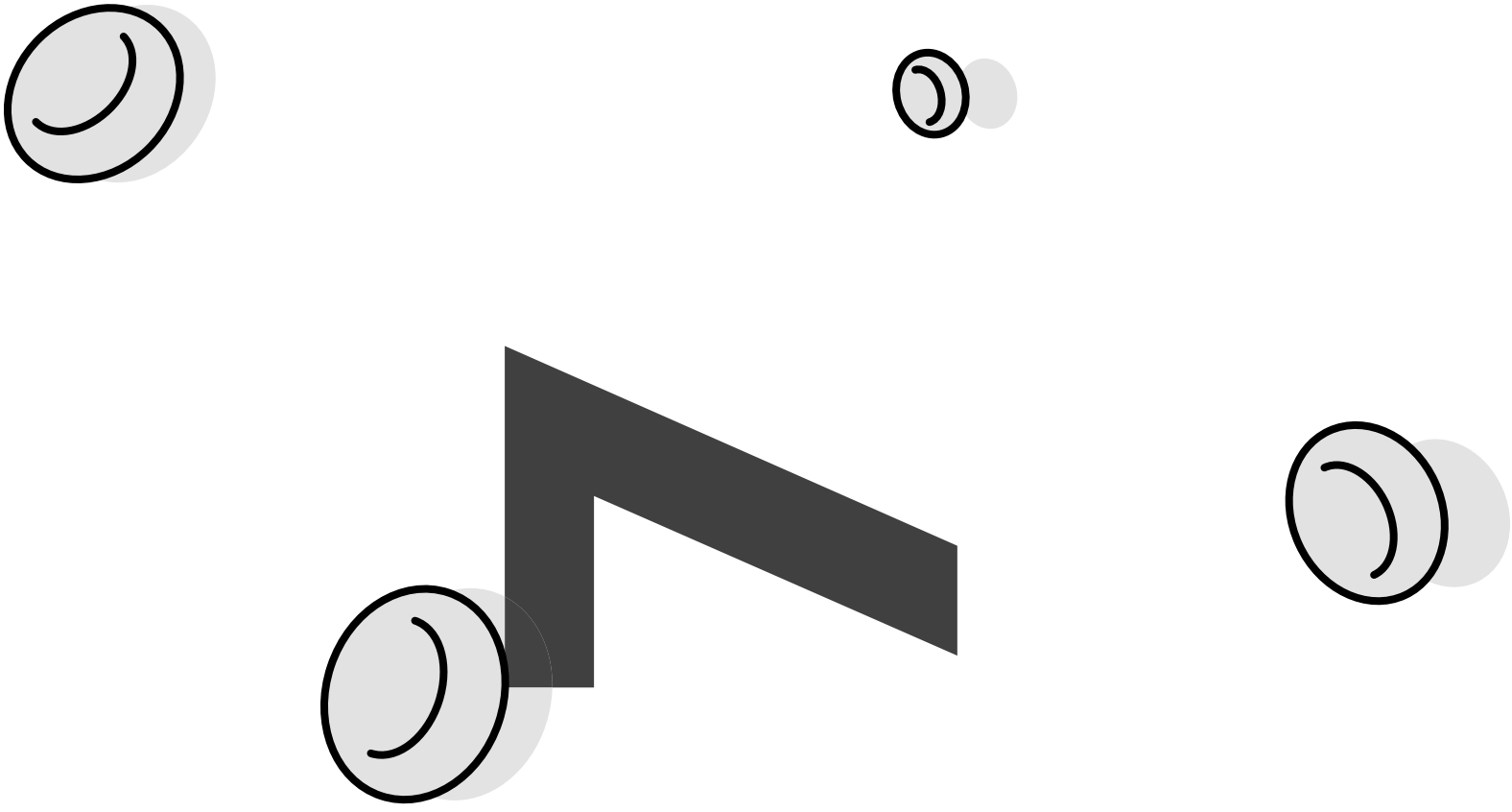
Bleeding type	LMWH Total no.	No therapy Total no.
Minor bleeding §		
Knee	8	1
Rectal bleeding	1	4
Menstruation (heavier than normal)	2	1
Throat	1	0
Anal bleeding	2	0
Head, arm	2	1
Leg, foot	1	0
Unknown	1	1
Total	18	7
Nose bleeding §	25	17
Hematoma >3cm §	26	15
Spontaneous hematoma >3cm*	17	8
Hematoma on head or trunk >3cm*	10	4
Grand Total	71	43

† *defined according to the ISTH guidelines (JTH 2010;8:202-4)*

‡ *defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, (temporary) cessation of study treatment, or associated with discomfort such as pain, or impairment of activities of daily life.*

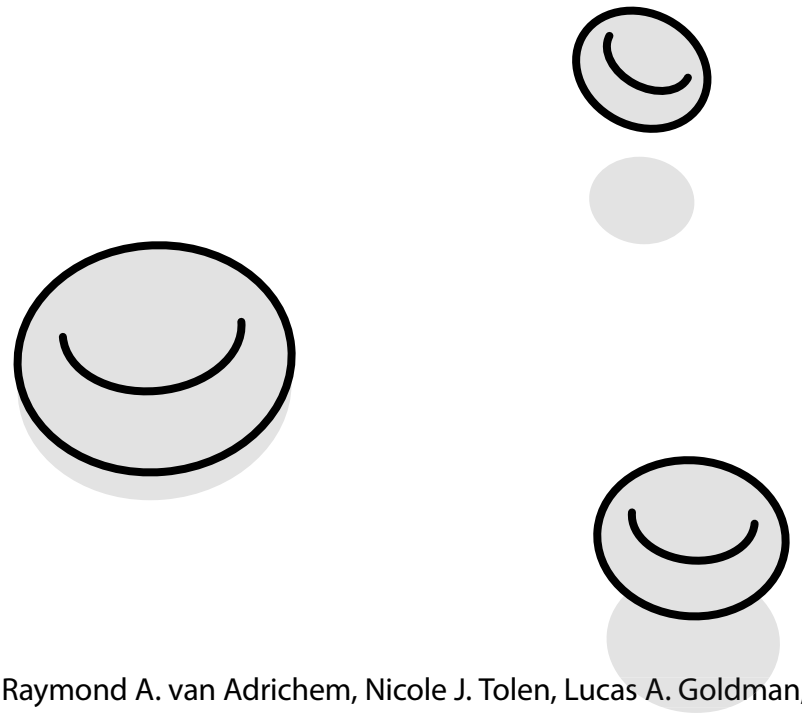
§ *defined as other bleeding not meeting the criteria for major or clinically relevant bleeding, no contact with a physician.*

**Does not add up as patients could have both conditions.*



CHAPTER

Venous thromboembolism prevention after anterior cruciate ligament reconstruction: compression stocking with and without low molecular weight heparin



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Submitted for publication

Abstract

Background

Evidence on the effectiveness of thromboprophylaxis in patients with anterior cruciate ligament reconstruction (ACL) is limited. Aim of this study was to establish the effect of low molecular weight heparin (LMWH) in addition to compression stockings after ACL reconstruction on venous thromboembolism (VTE) prevention.

Methods

Patients with ACL reconstruction between April 2011 and June 2013 in center A (compression stocking; n=441) and center B (compression stocking plus LMWH; n=936) were analyzed for the occurrence of VTE and bleeding events within three months. The clinics are located in the same geographical region and apply the same treatment protocol except for VTE prophylaxis. This observational design (e.g. an instrumental variable analysis) mimics a randomized trial. Cumulative incidences and risk differences (RD) with 95% confidence intervals (95CI) were calculated.

Results

One patient in center A (0.23%(95CI;0.01–1.41)) and four patients in center B (0.43%(95CI;0.12–1.14)) developed VTE, resulting in a RD of 0.20% (95CI;-0.41–0.81). In center A, five patients had a bleeding event (1.13%(95CI;0.41–2.71)) as did six patients in center B (0.64%(95CI;0.26–1.43)) resulting in a RD of -0.49% (95CI;-1.61–0.62).

Conclusion

Incidences of VTE and bleeding were low in both centers. No effect of routine LMWH could be demonstrated on the prevention of VTE after ACL reconstruction in addition to prophylaxis with compression stockings. Considering the burden from treatment with LMWH, routine treatment with LMWH after ACL reconstruction in addition to a compression stocking should not be recommended.

Introduction

Venous thromboembolism (VTE; the composite of deep vein thrombosis and pulmonary embolism) is a major public health problem.[1,2] A major risk factor for VTE is orthopedic surgery. Hence, thromboprophylaxis is recommended for most orthopedic procedures.[3-5] However, for knee arthroscopy, guidelines recommend not to use routine thromboprophylaxis, based on several small trials with a low incidence of symptomatic VTE in control groups.[3,4, 6-12] A recently published much larger trial confirmed this recommendation for regular knee arthroscopy.[13]

Since arthroscopic assisted ACL reconstruction is a more invasive procedure and has longer duration of surgery, the risk of VTE is estimated to be higher (i.e. 4% in 8 weeks).[14,15] The benefits of anticoagulant treatment may therefore outweigh the risk of postoperative bleeding as well as the burden for these patients. However, only two trials aimed to evaluate the effect of thromboprophylaxis after ACL reconstruction but they included small study populations (36 and 175 patients).[7,8] In addition, the later trial all focusses on short course vs extended prophylaxis.[8]In two other trials, patients with ACL reconstruction were included as a subset of patients with arthroscopic knee surgery (15 out of 241 patients and 681 out of 1761 patients), but patients with an ACL reconstruction were not analyzed separately.[6, 12] Furthermore in all studies the primary endpoint was the surrogate endpoint asymptomatic VTE. Unfortunately, the surrogate endpoint asymptomatic VTE is not representative of symptomatic VTE as no constant relationship was demonstrated between asymptomatic and symptomatic events in large VTE prevention trials.[16]

It is therefore currently unclear if thromboprophylaxis effectively reduces the risk of symptomatic VTE in these patients. This has resulted in variation in VTE prophylaxis policies in different centers that perform ACL reconstruction,[17] which variation provides a rare opportunity to study the effect of prophylactic Low Molecular Weight Heparin (LMWH) after ACL reconstruction in an observational setting that closely resembles a randomized trial, i.e., an instrumental variable analysis. An instrumental variable is a factor that affects the type of treatment a patient receives, but is not related to the patient's prognosis. Therefore, it mimics the randomization procedure in a randomized trial.[18-20]

In two clinics in The Netherlands, less than 10km apart, different VTE prophylaxis policies were used: in clinic A, virtually all patients received solely a compression stocking whilst in clinic B, all patients received both a compression stocking plus prophylactic LMWH. Similar patient populations were treated in these clinics, and the ACL reconstruction protocols were identical except for VTE prophylaxis.

In this setting, we aimed to study the effect of pharmacological thromboprophylaxis in addition to prophylaxis with compression stockings after arthroscopically assisted ACL reconstruction on prevention of VTE and the possibility of inducing bleeding events. The results of this study can aid clinicians in decision making on post-operative pharmacological prophylaxis after ACL reconstruction.

Methods

Study population

All patients who had an arthroscopically assisted ACL reconstruction between 1 April 2011 and 1 June 2013 in two clinics for orthopedic surgery (Orthopedium, Delft, the Netherlands, (center A; compression stocking, additional LWMH only in a few high-risk patients) and Medinova Zestienhoven, Rotterdam, the Netherlands, (center B; compression. stocking and LMWH)) were included in this study. The patients were selected using the ACL reconstruction operation code and the ACL rupture diagnosis code in the clinics' database. Only patients with an American Society of Anesthesiologists (ASA) physical status classification score of 1 or 2 were operated in these clinics due to limited intensive care possibilities available. There were no exclusion criteria for this study. Description of the assumptions for an instrumental variable which would allow any difference in occurrence of thromboembolic events between the two centers to be attributed to the difference in pharmacological thromboprophylaxis are described in the supplement. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center.

Surgery and protocols

All arthroscopically assisted ACL reconstructions were performed in outpatient care. Surgery details and mobilization protocol can be found in the supplement. Clinical follow-up consisted of a visit to the outpatient clinic 14 days, 6 weeks and 3 months post-operatively in both clinics.

Thromboprophylaxis

In center A all patients received a compression stocking (foot to thigh) to wear day and night on the operated leg for six weeks. Post-operative pharmacological thromboprophylaxis was only rarely provided to patients the surgeon believed to be at high risk for VTE (nadroparin 2850 IE once daily <100kg or nadroparin 5700 IE once daily ≥ 100 kg for two weeks). The thromboprophylaxis protocol in center B consisted of a compression stocking (foot to thigh) to wear in the daytime on the operated leg for six weeks plus LMWH once daily for 15 days post-operatively (nadroparin 2850 IE <80 kg once daily or nadroparin 5700 IE ≥ 80 kg once daily).

Data collection

Data were collected from the patient records which consisted of charts, intake forms, anesthesia reports, surgery reports, computer log files and the clinics complication registries. Details on collected data can be found in the supplement.

Endpoints

The primary outcome was symptomatic VTE in the 3 months after ACL reconstruction (confirmed by compression ultrasound or spiral CT pulmonary angiogram). The primary safety outcome was bleeding (major bleeding or other clinically relevant non major bleeding) according to the definition of the International Society of Thrombosis and Haemostasis in the 3 months after the procedure[21]. The secondary safety outcome was surgical site infection (i.e. superficial incisional surgical site infection, deep incisional surgical site infection, organ/ space surgical site infection) according to the definition of the Centers for Disease control and Prevention[22].

Confirmation of events

All patients with a VTE event in the Netherlands were treated in outpatient anticoagulation clinics at the time. To ensure no thrombotic events were missed, our dataset was linked to the records of the anticoagulation clinics to determine if any of the patients from the two clinics had been treated for a VTE event in the three months after surgery.

Sample size

Assuming a 4% VTE risk after ACL reconstruction[8, 14] and a risk reduction of 75% with treatment with low molecular weight heparin[6, 23] a sample size of 424 patients in each

arm would be sufficient (alpha 0.05 and power 80%) in a classic prospective randomized controlled trial (RCT). Considering the similar situation in which the two centers of our instrumental variable analysis resemble the treatment arms of a trial and the difference in treatment received between arms is expected to be close to 100%, the same sample size calculation for an RCT is applicable here too.

Statistical analysis

After completing data collection, data were exported to a SPSS database (IBM SPSS Statistics 20.0, IBM, Armonk, New York, US). From patients with multiple reconstructions during the study period only the first reconstruction was included in the analysis. Demographic and baseline data were summarized as means with standard deviation for normally distributed data, as medians with ranges for skewed distributed data or as proportions for categorical data. Bleeding complications were categorized as major bleeding or other clinically relevant non major bleeding. Surgical site infections were categorized as superficial incisional surgical site infections, deep incisional surgical site infection, organ/space surgical site infections. Cumulative incidences with 95% confidence intervals (95CI) for VTE, bleeding and surgical site infections in the three months after the procedure were estimated for both patient cohorts and compared by estimating the risk difference (RD) and relative risk (RR) with 95%CIs.

Results

Baseline characteristics

Using the diagnosis and operation codes for ACL rupture and reconstruction, a total of 454 procedures were identified in center A (compression stocking) and 969 were identified in center B (compression stocking and LMWH). In total, 441 patients of center A and 936 patients from center B were included in the analysis (see figure 1 for flow chart). The demographics of these patients are shown in table 1.

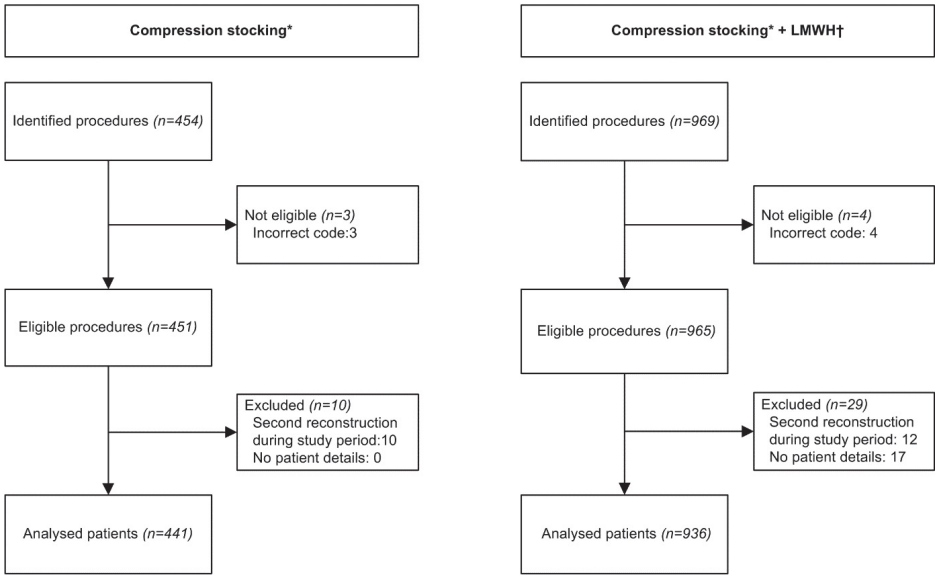

Figure 1. *Flow chart of patients*

Flow chart of patients identified in each clinic and included in the analysis.

**. Compression stocking foot to thigh*

†. Low molecular weight heparin

Table 1. *Characteristics of study population*

Patient characteristics	Compression stocking* (n=441)	Compression stocking* + LMWH†(N=936)
Male sex, n (%)	283 (64.2)	650 (69.4)
Median age, years (range)	29.0 (14.4 – 64.1)	26.9 (14.3 – 60.5)
Mean height, meters (SD)	1.78 (0.09)	1.79 (0.09)
Mean weight, kg (SD)	78.0 (13.0)	77.8 (12.2)
Median BMI‡, kg/m^2 (range)	24.1 (17.0 – 38.6)	24.2 (17.8 – 34.2)
BMI‡≥30, n (%)	24 (5.4)	29 (3.1)
ASA§ classification		
ASA§ 1, n (%)	375 (85.0)	690 (73.7)
ASA§ 2, n (%)	50 (11.3)	246 (26.3)
Left knee¶, n (%)	232 (52.6)	445 (47.5)
Smoking**, n (%)	95 (21.5)	248 (26.5)
Median units smoked daily, n (range)	10 (1 – 40)	10 (1 – 30)
Alcohol use††, n (%)	304 (68.9)	470 (50.2)
Median alcohol units weekly, n (range)	5 (1 – 40)	7 (1 – 28)
Pregnant during operation, n (%)	2 (0.5)	1 (0.1)
Recent surgery‡‡, n (%)	37 (8.4)	27 (2.9)
Non orthopedic surgery§§, n (%)	2 (0.5)	0 (0)
Orthopedic surgery¶¶, n (%)	35 (7.9)	26 (2.8)
Use of anticoagulants***, n (%)	0 (0)	2 (0.2)
Platelet inhibitors, n (%)	3 (0.7)	1 (0.1)
Hormonal replacement therapy	0 (0)	0 (0)
Previous episode of venous thrombosis†††, n (%)	3 (0.7)	14 (1.5)
Family history of venous thrombosis‡‡‡, n (%)	27 (6.1)	14 (1.5)
Orthopedic operation within 3 months after ACL§§§ reconstruction, n (%)	6 (1.4)	7 (0.7)
Comorbidities		
Hypertension, n (%)	17 (3.9)	20 (2.1)
Asthma, n (%)	21 (4.8)	56 (6.0)
DM¶¶¶ 1 or 2, n (%)	4 (0.9)	2 (0.2)
Thyroid disease****, n (%)	5 (1.1)	2 (0.2)
Chronic inflammatory disease††††, n (%)	0 (0.0)	5 (0.5)

Table 1. *Characteristics of study population (continued)*

Patient characteristics	Compression stocking* (n=441)	Compression stocking* + LMWH†(N=936)
Comorbidities (continued)		
Heart disease ‡‡‡‡, n (%)	4 (0.9)	4 (0.4)
TIA§§§§, n (%)	1 (0.2)	0 (0.0)
Malignancy, n (%), n (%)	1 (0.2)	2 (0.2)
Coagulation disorder ¶¶¶¶, n (%)	0 (0.0)	1 (0.0)
Varicose veins, n (%)	0 (0.0)	4 (0.4)
Hemolytic anemia, n (%)	0 (0.0)	1 (0.1)
Other*****, n (%)	22 (5.0)	35 (3.7)

* *Compression stocking foot to thigh*

† *LMWH: Low molecular weight heparin*

‡ *BMI: body mass index in kg/m^2. Of 5 patients in Center A no information on BMI was available.*

§ *ASA classification: American Society of Anesthesiologists physical status classification system. Of 16 patients in Center A the ASA classification could not be retrieved.*

¶ *Of 3 patients in center A the side of operation could not be retrieved*

** *Of 7 patients in center A smoking status could not be retrieved*

†† *Of 7 patients in center A Alcohol use could not be retrieved*

‡‡ *Surgery within 3 months before anterior cruciate ligament reconstruction. Of 7 patients in center A information on recent surgery could not be retrieved*

§§ *Surgery within 3 months before anterior cruciate ligament reconstruction, e.g. colonoscopy, endocervical curettage. Of 5 patients in center A no information on recent non-orthopedic surgery could be retrieved*

¶¶ *Orthopedic surgery within 3 months before anterior cruciate ligament reconstruction. e.g. diagnostic arthroscopy, meniscectomy, meniscal suture, arthroscopic debridement or lavage. Of 2 patients in Center A information on recent orthopedic surgery could not be retrieved*

*** *Of 4 patients in Center A information on the use of anticoagulants could not be retrieved*

††† *Either deep vein thrombosis or pulmonary embolism. Of 4 patients in Center A Information on a previous episode of venous thrombosis could not be retrieved.*

‡‡‡ *Either deep vein thrombosis or pulmonary embolism. Of 7 patients in Center A Information on family history of venous thrombosis could not be retrieved.*

§§§ *ACL: Anterior cruciate ligament reconstruction*

¶¶¶ *DM: diabetes mellitus*

**** *Either hyperthyroidism or hypothyroidism*

†††† *E.g. chronic inflammatory bowel disease*

‡‡‡‡ *Myocardial infarction and atrial fibrillation*

§§§§ *TIA: transient ischemic attack*

¶¶¶¶ *von Willebrand disease*

***** *E.g. hypercholesterolemia, migraine, attention deficit hyperactivity disorder.*

Surgical details

Mostly, the ACL reconstruction was performed under general anesthesia with the use of a thigh tourniquet and an autologous hamstring graft (table 2). In center A 19 patients (4.3%) were additionally treated with LMWH post-operatively because the surgeon believed they were at high risk of VTE (mainly previous episode of VTE (3 (0.7%)), family history of VTE (4 (0.9%)), obesity (5 (1.1%)), recent surgery (5 (1.1%))).

Table 2. *Surgery details*

Surgery details	**Compression stocking* (n=441)**	**Compression stocking* + LMWH† (N=936)**
Anesthesia‡:		
General, n(%)	365 (82.8)	923 (98.6)
Spinal, n(%)	68 (15.4)	13 (1.4)
Additional femoral block, n(%)	54 (19.0)	3 (0.3)
Procedure:		
Hamstring, n (%)	340 (77.1)	892 (95.3)
Bone-Patellar-tendon-bone, n(%)	77 (17.5)	31 (3.3)
Donor tendon, n(%)	24 (5.4)	13 (1.4)
Additional procedure:		
Meniscectomy, n(%)	99 (22.4)	351 (37.5)
Meniscal suture, n(%)	19 (4.3)	41 (4.4)
Microfracture, n(%)	2 (0.5)	2 (0.2)
Chondroplasty, n(%)	10 (2.3)	0 (0)
Tourniquet¶, yes (%)	421 (95.5)	934 (99.8)
Median tourniquet pressure, mmHg** (range)	300 (250 – 350)	300 (300 – 330)
Median tourniquet duration, minutes (range)	70 (30 – 140)	63 (39 – 140)

Table 2. *Surgery details (continued)*

Surgery details	Compression stocking* (n=441)	Compression stocking* + LMWH† (N=936)
ACL reconstruction rank ††		
Primary	435 (98.6)	934 (99.8)
Secondary	6 (1.4)	1 (0.1)
Tertiary	0 (0)	1 (0.1)
LMWH† after ACL†† reconstruction	19 (4.3)	934 (99.8)

** Compression stocking foot to thigh*

† LMWH: low molecular weight heparin

‡ Of 8 patients in center A information on type of anaesthesia could not be retrieved

§ Femoral block was used both in combination with general and spinal anaesthesia

¶ Of 7 patients in center A and 2 patients in center B information on tourniquet use could not be retrieved.

*** mmHg: millimeters of mercury*

†† ACL: anterior cruciate ligament

Venous thromboembolic events, bleeding and infections

The linkage with the database of the anticoagulation clinics was complete for 1057 (77%) patients, resulting in identification of one additional VTE event in center B and the confirmation of the other events.

Within three months after the procedure one VTE event occurred among the 441 patients in center A (compression stocking, cumulative incidence 0.23% (95CI; 0.01%–1.41%) (table 3). In two patients a diagnostic compression ultrasonography was conducted because of clinical suspicion of deep vein thrombosis, however, no thrombosis was diagnosed. In group B (compression stocking + LMWH) there were four events (cumulative incidence 0.43% (95CI; 0.12%–1.14%). The relative risk of VTE for patients treated with LMWH plus compression stocking compared to patients treated with a compression stocking alone was 1.9 (95CI; 0.2–11.8). The absolute risk difference was +0.20% (95CI; -0.41% – 0.81%). For further details of patients with a VTE see table 4.

Fewer bleeds were reported in the three months after the procedure in patients treated additionally with LMWH compared to compression stockings alone, (5 bleeds center A (1.13% (95CI; 0.41%–2.71%) and 6 in center B (0.64% (95CI; 0.26%–1.43%), RR 0.6 (95CI; 0.2–1.8)). Surgical site infections were reported more frequently in patients additionally treated with LMWH (1 in center A (0.23% (95CI; 0.01%–1.41%) and 9 in center B (0.96% (95CI; 0.48%–1.85%), RR 4.2 (95CI; 0.5–33.4). More details on major and minor bleeding and type of surgical site infection can be found in table 3.

Table 3. *complications*

Complication	Compression stocking* (n=441), n (%; 95CI)	Compression stocking* + LMWH† (N=936), n (%; 95CI)	RR (95CI)‡	RD (95CI), percentage points §
Venous thrombosis	1 (0.23; 0.01 – 1.41)	4 (0.43; 0.12 – 1.14)	1.9 (0.2 – 11.8)	0.20 (-0.41 – 0.81)
DVT¶	0 (0.00 – 1.04)	2 (0.21; 0.01 – 0.83)	∞	0.21 (-0.08 – 0.51)
DVT¶ and PE**	1 (0.23; 0.01 – 1.41)	1 (0.11; 0.01 – 0.67)	0.5 (0.03 – 7.5)	- 0.12 (-0.61 – 0.37)
PE**	0 (0.00 – 1.04)	1(0.11; 0.01 – 0.67)	∞	0.11 (-0.10 – 0.32)
Deceased	0 (0.00 – 1.04)	0 (0.00; 0.00 – 0.49)	-	0
Bleeding event	5 (1.13; 0.41 – 2.71)	6 (0.64; 0.26 – 1.43)	0.6 (0.2 – 1.8)	- 0.49 (-1.61 – 0.62)
Major Bleed	2 (0.45; 0.01 – 1.75)	0 (0.00; 0.00 – 0.49)	0	-0.45 (-1.08 – 0.17)
Minor Bleed	3 (0.68; 0.13 – 2.08)	6 (0.64; 0.26 – 1.43)	0.9 (0.2 – 3.8)	-0.04 (-0.96 – 0.88)
Surgical site infection	1 (0.23; 0. 01 – 1.41)	9 (0.96; 0.48 – 1.85)	4.2 (0.5 – 33.4)	0.73 (-0.03 – 1.50)
Superficial	0 (0.00 – 1.04)	5 (0.53; 0.19 – 1.28)	∞	0.53 (0.07 – 1.00)
Deep	0 (0.00 – 1.04)	4 (0.43; 0.12 – 1.14)	∞	0.43 (0.01 – 0.85)
Space (joint)	1 (0.23; 0.01 – 1.41)	0 (0.00; 0.00 – 0.49)	0	-0.24 (-0.67 – 0.22)

* *Compression stocking foot to thigh. No patients who received additional treatment with LMWH in center A developed a complication.*

† *LMWH: low molecular weight heparin*

‡ *RR (95CI): relative risk with 95% confidence interval*

§ *RD (95CI): absolute risk difference in percentage points with 95% confidence interval*

¶ *DVT: deep vein thrombosis*

** *PE: pulmonary embolism*

Table 4. *Description of patients with a venous thrombotic event*

Patient	Patients details	Surgery details	Time to event (in days)	Type of event
Centre A				
- Male, 43 years old	ASA* 1, BMI† 26.5, no known additional risk factors, no medication use	ACL‡ reconstruction (hamstring graft) + meniscectomy, general anesthesia, tourniquet use	22	DVT§ + PE¶
Centre B				
- Male, 39 years old	ASA* 1, BMI† 26.6, no known additional risk factors, no medication use	ACL‡ reconstruction (hamstring graft), general anesthesia, tourniquet use	27	DVT§
- Male, 40 years old	ASA* 1, BMI† 21.9, 2 units of alcohol consumption daily, no other known additional risk factors, no medication use	ACL reconstruction (hamstring graft), general anesthesia, tourniquet use	40	DVT§
- Male 42 years old	ASA* 1, BMI† 28.0, 1 unit of alcohol consumption daily, no other known additional risk factors, no medication use	ACL‡ reconstruction (hamstring graft), general anesthesia, tourniquet use	19	DVT§ + PE¶
- Male 30 years old	ASA* 2, BMI† 23.6, smokes 20 cigarettes daily, 1 unit of alcohol consumption daily, allergic rhinitis, use of antihistamine.	ACL‡ reconstruction (hamstring graft) + meniscectomy, general anesthesia, tourniquet use	14	DVT§

** ASA classification: American Society of Anesthesiologists physical status classification system*

† BMI: body mass index in kg/m²

‡ Anterior cruciate ligament

§ DVT: deep vein thrombosis

¶ PE: pulmonary embolism

Discussion

We found no reduced occurrence of symptomatic VTE with LMWH for 15 days in addition to a compression stocking for 6 weeks after ACL reconstruction (RR 1.9 (95CI; 0.2–11.8), comparing two centers with different VTE prophylaxis policies but otherwise identical treatment protocols and similar patient populations. Furthermore, the incidence of symptomatic VTE in both groups was low (0.23% vs 0.43%) and the corresponding absolute risk difference for treatment with LMWH was also low (RD +0.20% (95CI; -0.41%–0.81%)).

To our knowledge, only two randomized trials aimed to establish the effect of thromboprophylaxis with LMWH in patients with ACL reconstruction. Both trials included only small patient populations (36 and 175) and used asymptomatic VTE as the primary endpoint.[7,8] These studies were therefore largely underpowered and inconclusive for the clinically relevant endpoint, symptomatic VTE. Furthermore, the latter study addresses a different research question as it randomizes patients between short course vs extended thromboprophylaxis with LWMH[8]. In addition, in two trials addressing thromboprophylaxis after knee arthroscopy, also patients with an ACL reconstruction were included.[6, 12] However in one study, with only 6% of patients (15 out of 241) having an ACL reconstruction, the number of patients is limited.[12] In the other study the proportion of patients is much larger (39%(681 out of 1761 patients)), However in both trials patients with an ACL reconstruction were not analyzed separately.[6,12] Once more, asymptomatic VTE was used as the primary endpoint, limiting the ability to draw conclusions on the prevention of symptomatic VTE[16].

In the study on short course vs extended prophylaxis a much higher risk (4.4% in 3 to 4 weeks) of symptomatic VTE was found than in our study[8]. Patients in this study were hospitalized for 3 to 8 days after the reconstruction versus day-care surgery and direct mobilization in our study. The low incidence of VTE in our study is, however, in agreement with large database studies.[24, 25] The fact that all patients in our study were treated with a compression stocking may also have contributed to the low thrombosis risk found. The effect of compression stockings has been studied only on asymptomatic VTE in patients who had a total hip or knee arthroplasty. Here, the risk was reduced by compression stockings as shown in a meta-analysis of 6 trials (OR 0.47 (95CI; 0.32–0.68) for asymptomatic VTE and 0.44 (95CI; 0.12–1.58) for PE).[26]

In this study, preference in a center regarding prophylactic LMWH can be viewed as an instrumental variable, i.e. a factor that mimics randomization.[18, 20] In the supplement, we described the assumptions under which center preference for prophylactic LMWH would be a valid instrumental variable, i.e. when any difference in occurrence of VTE between the centers can be attributed to the difference in policy regarding LMWH. The first of these assumptions was clearly met with 95.8% of patients in center A treated with a compression stocking and 99.8% of patients in center B treated with compression stocking plus 15 days of LMWH. Although some confounders were unequally distributed between the centers (table 1), we expect the baseline risk of VTE (assumption 2) to be the same in both centers, because some risk factors for VTE were more frequent in center A, while others were more frequent in center B. On the whole, these risk factors are expected to balance each other out. With only five events in total, additional adjustments for unequally distributed confounders could not be made. Of note, a similar situation can occur in moderately sized randomized trials, where unequal distribution of prognostic factors can occur due to chance variation. Because pre-, per- and post-operative protocols were the same in both centers except for post-operative thromboprophylaxis, the assumption that center preference for LMWH may only affect VTE risk through LMWH administration (assumption 3) was also met. We are therefore confident we have provided a valid estimate of the treatment effect in the absence of a randomized trial. Regarding the low incidence of VTE, a regular trial, even using our most optimist effect of additional treatment with LMWH (e.g. a RR of 0.2 (lower level of the confidence interval), requires an unrealistically large number of 14.000 patients and should therefore be considered unfeasible (alpha 0.05 and power 80%). Therefore, we believe our study gives the most reliable results practical feasible considering pharmacologic thromboprophylaxis in patients with an ACL reconstruction.

As in all studies, including trials, some limitations need to be taken into account. Due to the limited intensive care possibilities in the clinics, only patients with an ASA classification of 1 or 2 were included in this study. This could potentially have implications for the generalizability of our results. However, the population of patients undergoing an ACL reconstruction consists in general of young, active and healthy persons. In a nationwide Danish study using the national knee ligament reconstruction registry, 94.5% of patients who received an ACL reconstruction had a Charlson comorbidity index of 0 (i.e. healthy patients , while only 0.2% of patients had an index of 3 or higher.[27] Therefore most likely only a few, if any, ASA 3 patients may have been referred to

another hospital so we believe this has had only a minor effect on the generalizability of our results.

Furthermore, results may have been influenced by a small difference in the compression stocking protocol between centers. In center A, patients were advised to wear their stocking for day and night, whereas in center B patients were advised to wear the stocking in daytime. However, a strong effect of this difference is unlikely as compression stockings are only effective in combination with muscle pump activity, which is clearly not present during the night. Additionally, a small proportion of patients (19 patients, 4.3%) were treated with LMWH in center A, due to a perceived high risk of VTE. Because these patients would have received LMWH in either center, our study provides no information on the effect of prophylactic LMWH in this high-risk subgroup. If we assume that these patients had an unusually high risk of 10% of developing VTE and if we assume that all events were prevented by the use of LMWH, 2 more cases of VTE would have been prevented. Adding these 2 extra cases to the results leads to a cumulative incidence of VTE in Centre A of 3/441= 0.68% (95CI; 0.13 – 2.08). With a corresponding RR of 0.63 (95CI; 0.18 – 2.20) and a RD of 0.25% (95CI; -0.62% - 1.13%), we still cannot show a clinically relevant and significant advantage of additional treatment with LMWH.

Because patients were not routinely screened for VTE, events could have been missed since the symptoms of VTE may mimic those after an ACL reconstruction. However, this corresponds to daily clinical practice. Furthermore, the clinical relevance of detecting asymptomatic events is questionable and not recommended for trials addressing the effect of thromboprophylaxis.[3,16] Events could also have been missed in the clinics in case VTE was treated elsewhere, unknown to the orthopedic surgeons. However, to ensure a complete follow-up of all patients and to guarantee no VTE events were missed, our database was linked to the databases of the national anticoagulation clinics. This linkage was complete for 77% of patients and led to identification of only one additional event. We were unable to perform such a linkage to databases for bleeding events or surgical site infections. Although patients were seen at the outpatient clinic 14 days, 6 weeks and 3 months post-operatively for follow up, these events may have been underreported.

In this study we were unable to demonstrate a beneficial effect of 15 days of treatment with LMWH. A possible explanation for this finding is that patients in both groups were treated with a compression stocking, perhaps already maximally lowering the thrombosis risk. In addition, the reconstructive surgery in both clinics was performed in day-care setting and patients were mobilized immediately post-operatively, further reducing their thrombosis risk. Lastly, the population of patients undergoing an ACL reconstruction is a young, active and healthy population, therefore the baseline risk of VTE in these patients is in general already low.[2]

On the basis of our findings it is justified to assume that there is no beneficial effect of routinely adding LMWH to prophylaxis with a compression stocking and early mobilization in these patients, while there may be clear disadvantages related to this treatment, such as the costs involved, the burden of daily injections and the risk of bleeding complications. Although we did not find an increased risk of bleeding for treatment with LMWH, an increased bleeding risk has been demonstrated in previous studies (RR1.73 (95CI; 1.09–2.73).[6, 28] We did find a small increase in surgical site infections in the group treated with LMWH. A possible explanation is prolonged wound drainage caused by anticoagulants, which may have an effect on primary wound healing. The latter has been suggested after total joint arthroplasty surgery.[29-30]

Conclusion

We were unable to demonstrate any benefit of routine treatment with LMWH in patients receiving an ACL reconstruction in addition to VTE prophylaxis with a compression stocking and early mobilization. With respect to our results, we would advise not to provide thromboprophylaxis, with its associated burden and risks, routinely to this generally young and healthy group of patients, in whom the risk is very low. Nevertheless, we cannot exclude that anticoagulant therapy might be beneficial in certain high-risk patients. Identifying high risk groups and selective treatment of these patients should be the aim of future studies, thereby reducing thrombosis morbidity and the risk of treatment complications.

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Supplement material

Instrumental variable assumptions

In order to ascribe any difference between center A and center B in occurrence of venous thromboembolism or another outcome to prophylactic LMWH, a number of assumptions for instrumental variable analysis should be met. The centers must differ in their preference for type of treatment (assumption 1), the prognosis regarding VTE risk of the patients in the centers must be the same (assumption 2) and center preferences must not influence the VTE risk by other pathways than VTE prophylaxis (such as co-medication or mobilization protocol, assumption 3)[1,2]. Both clinics are specialized orthopedic clinics and are in the same geographical area (less than 10 kilometers apart). In addition, both clinics use the same surgical technique, pre-, per-, and post-operative protocols (including mobilization protocol), except for post-operative pharmacological thrombosis prophylaxis. All three assumptions for an instrumental variable are therefore expected to hold, which would allow any difference in occurrence of thromboembolic events between the two centers to be attributed to the difference in pharmacological thrombosis prophylaxis.

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Surgery protocol

Patients were given pre-operative 2gr cefazolin, 75mg diclofenac and 1 gr paracetamol (acetaminophen) all intravenously. The reconstruction was performed using a hamstring autograft (semitendinous-gracilis), bone-patellar tendon-bone autograft or a donor graft. Post-operative pain protocol consists of 10 ml levobupivacaine 5mg/ml and 10 ml 1% adrenaline 1:200.000 intra articular. Patients were post-operatively prescribed 5 days paracetamol(acetaminophen) 1gr 4 times daily, meloxicam 7,5mg 2 times daily and, if necessary, tramadol 50-100mg 3 times daily and ondansetron 4mg 1 time daily (all orally). Patients who received a donor graft ACL reconstruction received prophylactic antibiotic treatment (three times 1gr cefazolin over 24hours) and patients with an increased risk of complications (e.g. BMI>30, comorbidities or procedure performed with donor graft) stayed overnight. Patients were allowed to mobilize immediately after

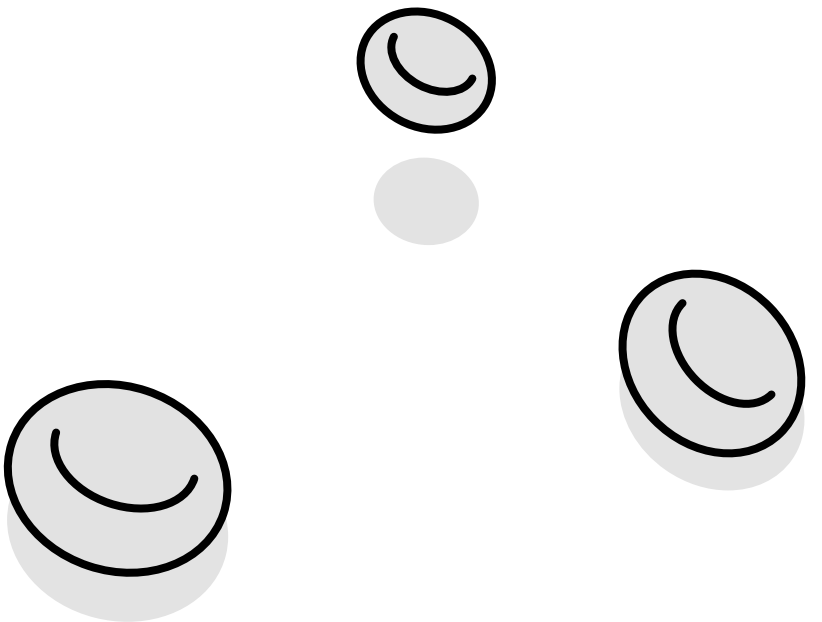
surgery with crutches for 4-6 weeks and received a referral for physical therapy for 4-6 months which could be started seven days after surgery.

Details on data collection

All collected data were coded and registered in an Access database (Microsoft Access 2010, Microsoft corporation, Redmond, Washington, US). Surgical details, such as reconstruction technique (hamstring graft, bone-patellar tendon-bone, or allograft) and duration of surgery were recorded. We registered if the reconstruction was a primary reconstruction, a second (or third) reconstruction or a revision of a previous (still intact, however unstable) ACL reconstruction and if there were any concomitant procedures performed (such as a meniscectomy or meniscal suture). Besides all the operation procedures, data such as location of residence, age, sex, BMI, alcohol use and smoking, medication use, co-existing diseases, medical history (including surgery three months prior to the reconstruction), follow-up information and postoperative complications were also recorded.

CHAPTER

Venous thrombosis risk after cast immobilization of the lower extremity: derivation and validation of a clinical prediction score, L-TRiP(cast), in three population-based case–control studies



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Abstract

Background

Guidelines and clinical practice vary considerably with respect to thrombosis prophylaxis during plaster cast immobilization of the lower extremity. Identifying patients at high risk for the development of venous thromboembolism (VTE) would provide a basis for considering individual thromboprophylaxis use and planning treatment studies.

The aims of this study were (1) to investigate the predictive value of genetic and environmental risk factors, levels of coagulation factors, and other biomarkers for the occurrence of VTE after cast immobilization of the lower extremity and (2) to develop a clinical prediction tool for the prediction of VTE in plaster cast patients.

Methods

We used data from a large population-based case–control study (MEGA study, 4,446 cases with VTE, 6,118 controls without) designed to identify risk factors for a first VTE. Cases were recruited from six anticoagulation clinics in the Netherlands between 1999 and 2004; controls were their partners or individuals identified via random digit dialing. Identification of predictor variables to be included in the model was based on reported associations in the literature or on a relative risk (odds ratio) > 1.2 and $p \leq 0.25$ in the univariate analysis of all participants. Using multivariate logistic regression, a full prediction model was created. In addition to the full model (all variables), a restricted model (minimum number of predictors with a maximum predictive value) and a clinical model (environmental risk factors only, no blood draw or assays required) were created. To determine the discriminatory power in patients with cast immobilization (n = 230), the area under the curve (AUC) was calculated by means of a receiver operating characteristic. Validation was performed in two other case–control studies of the etiology of VTE: (1) the THE-VTE study, a two-center, population-based case–control study (conducted in Leiden, the Netherlands, and Cambridge, United Kingdom) with 784 cases and 523 controls included between March 2003 and December 2008 and (2) the Milan study, a population-based case–control study with 2,117 cases and 2,088 controls selected between December 1993 and December 2010 at the Thrombosis Center, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy.

Results

The full model consisted of 32 predictors, including three genetic factors and six biomarkers. For this model, an AUC of 0.85 (95% CI 0.77–0.92) was found in individuals with plaster cast immobilization of the lower extremity. The AUC was the same for the restricted model (containing 11 predictors, including two genetic factors and one biomarker). The clinical model (consisting of 14 environmental predictors) resulted in an AUC of 0.77 (95% CI 0.66–0.87). The clinical model was converted into a risk score, the L-TRiP(cast) score (Leiden–Thrombosis Risk Prediction for patients with cast immobilization score), which showed an AUC of 0.76 (95% CI 0.66–0.86). Validation in the THE-VTE study data resulted in an AUC of 0.77 (95% CI 0.58–0.96) for the L-TRiP(cast) score. Validation in the Milan study resulted in an AUC of 0.93 (95% CI 0.86–1.00) for the full model, an AUC of 0.92 (95% CI 0.76–0.87) for the restricted model, and an AUC of 0.96 (95% CI 0.92–0.99) for the clinical model. The L-TRiP(cast) score resulted in an AUC of 0.95 (95% CI 0.91–0.99).

Major limitations of this study were that information on thromboprophylaxis was not available for patients who had plaster cast immobilization of the lower extremity and that blood was drawn 3 months after the thrombotic event.

Conclusions

These results show that information on environmental risk factors, coagulation factors, and genetic determinants in patients with plaster casts leads to high accuracy in the prediction of VTE risk. In daily practice, the clinical model may be the preferred model as its factors are most easy to determine, while the model still has good predictive performance. These results may provide guidance for thromboprophylaxis and form the basis for a management study.

Introduction

The incidence of venous thromboembolism (VTE) is estimated to be 1–2 per 1,000 person-years and increases with age up to 1% per year in the elderly.[1] An individual's lifetime risk for the development of VTE is about 11%.[1–3] Multiple genetic and environmental risk factors, including cast immobilization, have been identified in etiologic research. However, the presence of one risk factor is generally not sufficient for the development of a thrombotic event. Only when multiple risk factors have accumulated, some of which may interact in a synergistic way, and the "thrombotic threshold" is crossed will thrombosis occur.[1] Although we understand this mechanism in general, we cannot accurately predict which individuals will develop VTE.[3] Such knowledge would be of use, as it allows targeted thrombosis prevention.

Recently, Hippisley-Cox and Coupland developed a risk prediction algorithm to estimate future risk of VTE in the general population. This prediction model included 15 environmental risk factors and resulted in a receiver operating characteristic (ROC) area under the curve (AUC) statistic of 0.75.[4] Earlier, the Padua prediction score included similar risk factors in a risk assessment model for VTE in hospitalized medical patients.[5] In addition to these prediction models, which included only environmental predictors, there have been a few studies that investigated the added value of biomarkers. Recently, de Haan et al. developed a risk model that incorporated thrombosis-associated single nucleotide polymorphisms (SNPs) combined with environmental risk factors, which reached an AUC statistic of 0.82 in the general population.[6] The role of factor VIII, D-dimer, prothrombin fragment 1 + 2, platelet count, and hemoglobin level in predicting VTE has mainly been studied in patients with cancer.[7–9]

Using a prediction model for first VTE in the general population is not efficient considering the heterogeneity of the condition and the rarity of disease in the general population. However, in more homogeneous high-risk groups, such as patients with cast immobilization, prediction of VTE can be useful and cost-effective. Our recent study showed an 8-fold increased risk of VTE in patients with below-knee cast immobilization.[10] In terms of absolute risk, VTE incidence rates reported in these patients vary strongly depending on study design and definition of the event (asymptomatic or symptomatic). A recent meta-analysis reported a rate of symptomatic VTE during cast immobilization that varied between 0% and 5.5%.[11] The risk of VTE during cast immobilization is probably not large enough to justify anticoagulant prophylaxis in all

patients with plaster cast, as the bleeding risk will also be considerable (0.3% major bleeding).[12,13] Therefore, it would be beneficial to identify those at high risk and to offer targeted, individualized therapy.

The purpose of this study was to investigate the predictive value of genetic and environmental risk factors, coagulation factors, and other biomarkers for the development of VTE after cast immobilization of the lower extremity. We developed several models: in addition to a full model, we also created a restricted model in which we tried to find the optimal balance between maximum predictive value and a minimum number of (all types of) predictor variables and a clinical model that contained only predictors that are easy to determine in clinical practice. Finally, we validated the models in two independent datasets.

Methods

Study Design

For developing the model, data from a large population-based case–control study, the MEGA study (Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis) were used (see supplement material, analysis plan). Details of this study have been published previously.[14–16] In short, 4,956 consecutive patients aged 18 to 70 y with a first deep vein thrombosis (DVT), pulmonary embolism (PE), or both were recruited from six anticoagulation clinics in the Netherlands between 1 March 1999 and 31 August 2004. The diagnosis of DVT or PE was confirmed by (Doppler) ultrasonography, ventilation/perfusion scan, angiography, or spiral CT scan. The control group (n = 6,297) consisted of partners of participating patients and other controls who were identified using a random digit dialing method; controls were frequency matched to cases with respect to sex and age. Approval for this study was obtained from the Medical Ethics Committee of the Leiden University Medical Center, and all participants provided written informed consent.

Data Collection and Laboratory Analysis

All participants completed a questionnaire on risk factors for VTE that included questions on (potential) risk factors such as trauma, immobilization (including plaster cast and location), (orthopedic) surgery, current use of (any) medication, and comorbidity in the past year before the venous thrombotic event.

In patients and controls included from the start of the study until May 31, 2002, a blood sample was collected approximately 3 months after discontinuation of oral anticoagulant therapy. In patients who were still on anticoagulant therapy 1 y after the event, blood was drawn during treatment. Detailed information on laboratory analyses of coagulation factors and hemorheological and other markers can be found in the supplement material. For patients and controls included after June 1, 2002, and for patients who were unable to visit the clinic, DNA was collected by means of buccal swabs sent by mail. The factor V Leiden (F5, rs6025) and prothrombin G20210A (F2, rs1799963) mutations were measured simultaneously by a multiplex polymerase chain reaction using the TaqMan assay.[17] ABO blood type was also analyzed using the TaqMan assay.[18]

Model Derivation

Development of the full prediction model

All prediction models were developed using the whole MEGA study population, with the exclusion of 689 individuals with multi-trauma, plaster cast of the arm or back, plaster cast after the occurrence of thrombosis, or use of anticoagulation medication during blood collection. In total, 4,446 cases and 6,118 controls were included in the analysis. Multiple imputation techniques were used for missing values. In the imputation step, skewed variables were transformed (five datasets were imputed, and results were pooled according to Rubin's rules).[19]

Because the subset of individuals with plaster cast was small (n = 230), we were not able to test our model without imputed data in this specific group. Too many patients were missing one or more variables, and logistic regression analyses were not possible. However, results were consistent in the entire MEGA study population with and without the imputed data. Moreover, we checked all imputed data for errors. Univariate regression for all predictors was similar in the entire MEGA population when we performed regression analyses with and without imputed data. Additional information on missing data can be found in the supplement material.

Controls were frequency matched on age and sex, meaning that the age and sex distribution of the control group was similar to that of the patient group. The age and sex distribution of the control group was therefore different from that of the general population (e.g., relatively older age and more females). In order to use age and sex as predictor variables, we needed a control group in which the age and sex distribution

reflected the general population. For this we weighted the control individuals (for age and sex) to the age and sex distribution of the Dutch population in 2001 (Statistics Netherlands). Weights were calculated by dividing the proportion of individuals in a certain age- and sex-specific stratum in the Dutch population by the stratum-specific proportion of individuals in the MEGA study control group. For example, in the Dutch population, 1.2% of all inhabitants aged 18 and 70 y (same age range as our study) were 30-y-old males. In the MEGA study, this proportion was 0.8%, giving these individuals in our study a weight of 1.5 (1.2% divided by 0.8%). This approach is called direct standardization. Using this approach, younger control individuals were assigned a weight above one, and older control individuals were assigned a weight below one. This way we corrected for the "oversampling" of older control individuals (due to frequency matching) and created a control group with the same age and sex distribution as that of the Dutch population in 2001. We subsequently performed weighted logistic regression analyses incorporating age and sex as predictor variables in our prediction model.

Derivation process

For the development of the derivation models, the whole MEGA study population was used rather than the plaster cast subgroup, to avoid overfitting in the derivation process. Fig. 1 shows a flowchart of the model derivation process. Identification of candidate predictor variables (see Table 1) was based on (1) reported associations with the occurrence of VTE in the literature and standardized and easy measurement or (2) finding an odds ratio (OR) > 1.2 (highest versus lowest category) and a p-value ≤ 0.25 between cases and controls in the overall MEGA study population using weighted logistic regression (Fig. 1, step 1). Continuous predictors such as age and body mass index (BMI) were categorized, biomarker values were split into tertiles based on control individuals, and protein S and protein C antigen levels were dichotomized (< 65 versus ≥65 IU/dl). The variable "plaster cast" was classified as no plaster cast, complete leg cast, lower leg cast, circular knee cast, or foot cast, resulting in discrimination between different locations (more/less immobilization). Related clinical factors with a similar OR in the multivariate model were combined into one variable. The variables rheumatoid arthritis, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and multiple sclerosis were combined into the variable "comorbidity"; previous heart attack and angina pectoris into "cardiovascular disease"; stroke and transient ischemic attack (TIA) into "cerebrovascular events"; and urinary tract infection/cystitis,

pyelonephritis, arthritis, bursitis, inflammation of other body parts, and tropical diseases into “inflammatory disease.”

The full prediction model was created using a forward selection procedure (entry $p < 0.05$) with the candidate biomarkers and genetic and clinical variables. Of all the variables that were not included in the model by this forward selection, some predictors were nevertheless retained in the full model because of a well-established reported association with the occurrence of VTE in the literature (Fig. 1, step 2).

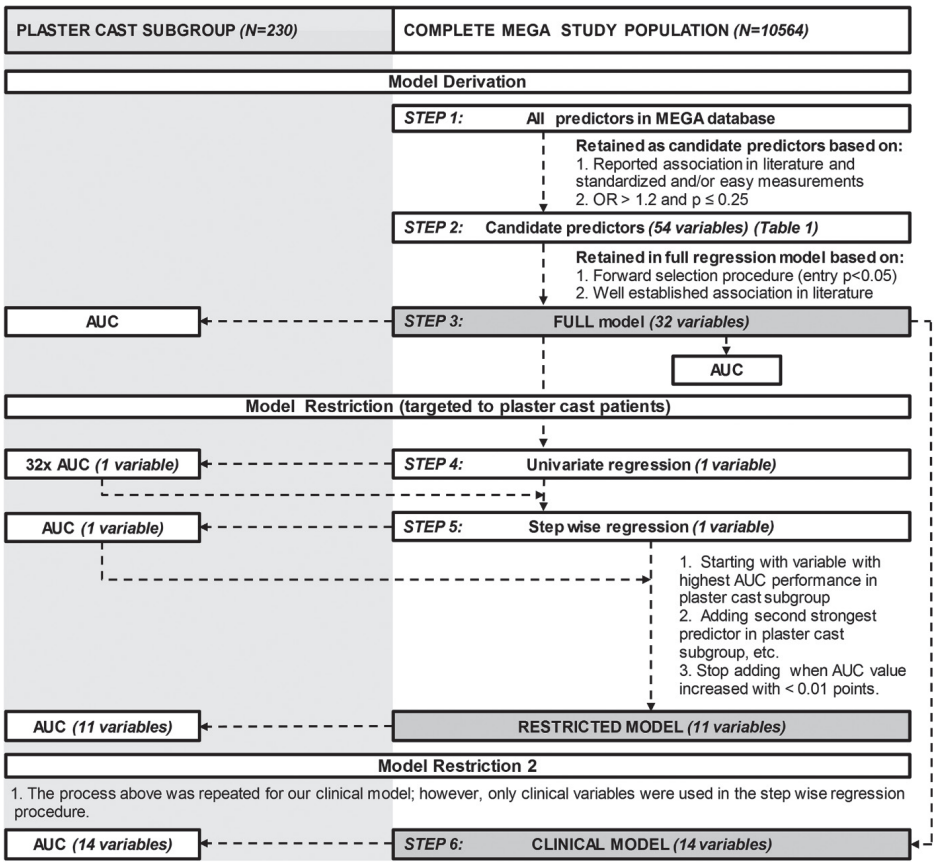

Figure 1. *Flowchart of the prediction model derivation process*

Table 1. *Candidate predictor variables*

Category	Candidate Predictor Variable
Environmental predictor variables	Age
	Sex
	Smoking
	Varicose veins
	Cancer within the past 5 y
	Congestive heart failure
	Comorbidity (rheumatoid arthritis, chronic kidney disease, COPD, multiple sclerosis)
	Cardiovascular disease (heart attack and angina pectoris)
	Cerebrovascular events (stroke and TIA)
	BMI
	Claudication
	Family history of VTE (first-degree relative)
	Hospital admission within the past 3 mo
	Bedridden within the past 3 mo
	Paralysis (partial)
	Surgery within the past 3 mo
	Current pregnancy or puerperium
	Current use of antipsychotic medication
	Current use of tamoxifen
	Current use of hormonal replacement therapy
	Current use of oral contraceptives
	Superficial vein thrombosis
	Plaster cast and location (no plaster cast, complete leg cast, lower leg cast, circular knee cast, or foot cast)
	Hepatitis
	Pneumonia
	Inflammatory disease (urinary tract infection/cystitis, pyelonephritis, arthritis, bursitis, inflammation of other body parts, and tropical diseases)

Table 1. *Candidate predictor variables (continued)*

Category	Candidate Predictor Variable
Hemorheologic and coagulation predictor variables	Fibrinogen activity
	Factor VIII activity and antigen level
	Von Willebrand factor antigen level
	Factor IX antigen mean
	Protein S antigen mean
	Factor II activity
	Factor VII activity
	Factor X antigen level
	Protein C activity
	Factor XI activity
	Hematocrit
	White blood cell count
	Percentage/number lymphocytes
	Percentage/number monocytes
	Percentage/number granulocytes
	Red blood cell count
	Hemoglobin level
	Mean cell volume
	Mean cell hemoglobin
	Mean cell hemoglobin concentration
	Red cell distribution width
	Antithrombin activity
	Total homocysteine
	Total cysteine
	Methionine
Genetic predictor variables	Factor V Leiden mutation
	Prothrombin mutation
	Non-O blood type

Calculating the discriminative value

To determine the magnitude of discrimination of this model, an AUC (c-statistic) was calculated by means of a ROC, based on the predictions from the multiple logistic regression models. ROC curves were created both in the entire study population and in the plaster cast subgroup only, for which regression coefficients of the model developed in the total MEGA study population were used (Fig. 1, step 3).

Model Restriction

Models targeted to plaster cast patients: clinical and restricted models

From this full model, we developed two reduced sub-models specially targeted to plaster cast patients, i.e., the restricted model and the clinical model. For the development of the restricted model, we used as candidate variables the 32 variables included in our full model (including biomarkers and genetic variables). We performed a forward selection procedure. Models were fitted using all MEGA study individuals, but variables were selected based on the increase in AUC in the plaster cast subset of patients. This means that we started by fitting all 32 variables separately with a univariate logistic regression analysis using all MEGA study individuals. For each of the 32 predictors, we calculated the AUC in the subgroup of plaster cast patients (Fig. 1, step 4). The variable corresponding to the highest AUC was then selected in the model (Fig. 1, step 5). This procedure was repeated by subsequently adding the next strongest predictor until the AUC value in the plaster cast population increased by less than 0.01 points. Age and sex were forced (at first) in the model because of clinical importance. Variables were also selected based on their availability in our validation cohorts. For instance, when two variables performed the same in our plaster cast subgroup in the MEGA study, we chose to select the predictor that was also available in our validation cohorts. The model obtained in this way is the restricted model.

The clinical model was developed in the same way as the restricted model with the exception that only environmental predictor variables from the full model were used. Biomarkers and genetic variables were not included (Fig. 1, step 6).

In this way we were able to develop models targeted to the plaster cast subpopulation, while the regression coefficients were stable because they were derived from the entire MEGA population.[20]

Clinical risk score for plaster cast patients: the L-TRiP(cast) score

Additionally, we developed a risk score, the L-TRiP(cast) score (Leiden–Thrombosis Risk Prediction for patients with cast immobilization score), in which risk points are based on the regression coefficients (betas) for predictor variables in the clinical multivariate logistic model. We used the following scoring: 0.20 < beta ≤ 0.75, 1 point; 0.75 < beta ≤ 1.25, 2 points; 1.25 < beta ≤ 1.75, 3 points; 1.75 < beta ≤ 2.25, 4 points; beta > 2.25, 5 points. The L-TRiP(cast) score was the sum of these points across the predictor variables. The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated for different cutoff points of the L-TRiP(cast) score assuming an incidence of 2.5% for VTE in plaster cast patients, which is the reported incidence from a Cochrane meta-analysis.[13]

Model validation

Validation was performed in two other case–control studies of the etiology of VTE: the THE-VTE study[21,22] and the Milan study[23] (both published in detail previously). The THE-VTE study is a two-center, population-based case–control study that was performed in Leiden, the Netherlands, and Cambridge, United Kingdom. Valid information on all environmental risk factors was available for all 784 cases and 523 controls who were enrolled in the study between March 2003 and December 2008. The Milan study is also a population-based case–control study: 2,117 cases and 2,088 controls were enrolled between December 1993 and December 2010 at the Thrombosis Center, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy. In addition to information on environmental risk factors, data on biomarkers and genetic predictors were collected in this study. In the Milan study, all genetic predictors and factor VIII activity were measured, and most environmental risk variables were known. Only Von Willebrand factor antigen level, red cell distribution width, percentage of monocytes, factor XI activity, and total cysteine were not available. In the Milan study, the following variables were not recorded: cancer within the past 5 years, comorbidity, cerebrovascular events, hospital admission within the past 3 months, paralysis, pregnancy, superficial vein thrombosis, hepatitis, and pneumonia. The variable smoking was coded as yes/no, family history of VTE was coded as yes/no, and information on type of plaster cast of the lower extremity (i.e., complete versus lower leg) was not available. For each individual, the different prognostic scores were calculated using the regression coefficients derived in the MEGA study.

Analyses were performed in IBM SPSS Statistics for Windows, version 20.0. The weighted analyses were performed in Stata, version 12.

Results

Study Population

In the model derivation analysis, 4,446 cases and 6,118 controls were included. Of the cases, 2,606 (58.6%) were diagnosed with DVT, 1,452 (32.7%) had PE, and 388 (8.7%) had both. Plaster cast immobilization of the lower extremity was present in 194 patients and 36 control individuals, mainly due to traumatic events. Among these patients, 131 (67%) individuals developed DVT, 44 (23%) PE, and 19 (10%) both. The predictors that had the highest prevalence among cases were smoking, presence of varicose veins, being overweight, family history of thrombosis (first-degree relative), use of oral contraceptives, cancer in the past 5 y, and comorbidity. Frequencies of these variables in controls were much lower. Further baseline characteristics, including coagulation markers and genetic predictor variables, can be found in the supplement material.

Model Derivation

In univariate analyses, all 54 candidate predictor variables were significantly ($p < 0.25$) associated with the occurrence of VTE, with the exception of protein S antigen, percentage/number of lymphocytes and granulocytes, hemoglobin level, total homocysteine and antithrombin activity.

Out of these candidate predictors, 32 variables were retained in our full prediction model; these variables are listed in Table 2. The predictors cerebrovascular events, congestive heart failure, hepatitis, current use of tamoxifen, and non-O blood type were not significantly associated with VTE. Nevertheless, these were retained in the model because of a clear association with VTE in the literature. Factors most strongly associated with VTE, e.g., with the highest relative risk in this full model, were cancer within the past 5 y (OR 4.8, 95% CI 3.6–6.5), hospital admission within the past 3 months (OR 3.6, 95% CI 2.7–4.7), current use of oral contraceptives (OR 7.3, 95% CI 6.0–8.8), pregnancy or puerperium (OR 6.1, 95% CI 4.0–9.5), complete leg plaster cast (OR 11.1, 95% CI 4.0–30.8), and factor V Leiden mutation (OR 5.7, 95% CI 1.6–19.7). Additional details on the univariate and multivariate ORs for the full logistic regression model in the MEGA study population can be found in the supplement material. The

discriminatory value of the full regression model resulted in an AUC of 0.85 (95% CI 0.77–0.92) in plaster cast patients and 0.88 (95% CI 0.87–0.89) in the entire MEGA population (Table 3).

Table 2. *Overview of predictor variables in each model*

Category	Predictor Variable	Model		
		Full	Restricted	Clinical
Environmental predictor variables	Age	×	×	×
	Sex	×	×	×
	BMI	×	×	×
	Smoking	×		
	Varicose veins	×		
	Cancer within the past 5 y	×		×
	Congestive heart failure	×		
	Comorbidity (rheumatoid arthritis, chronic kidney disease, COPD, multiple sclerosis)	×		×
	Cerebrovascular events (stroke and TIA)	×		
	Family history of VTE (first-degree relative)	×	×	×
	Hospital admission within the past 3 mo	×		×
	Bedridden within the past 3 mo	×	×	×
	Paralysis (partial)	×		
	Surgery within the past 3 mo	×	×	×
	Pregnancy or puerperium	×		×
	Current use of antipsychotic medication	×		
	Current use of tamoxifen	×		
	Current use of hormonal replacement therapy	×		
	Current use of oral contraceptives	×	×	×
	Superficial vein thrombosis	×		×
	Hepatitis	×		
	Pneumonia	×		×
	Plaster cast and location (no plaster cast, complete leg cast, lower leg cast, circular knee cast, or foot cast)	×	×	×

Table 2. *Overview of predictor variables in each model (continued)*

Category	Predictor Variable	Model		
		Full	Restricted	Clinical
Hemorheological and coagulation predictor variables	Factor VIII activity	×	×	
	Von Willebrand factor antigen level	×		
	Factor XI activity	×		
	Percentage of monocytes	×		
	Total cysteine	×		
	Red cell distribution width	×		
Genetic predictor variables	Factor V Leiden mutation	×		
	Prothrombin mutation	×	×	
	Non-O blood type	×	×	

Table 3. *AUC values of the full, restricted and clinical models, both in all individuals and in the plaster cast subgroup*

Model	All individuals		Plaster Cast Subgroup	
	AUC	95% CI	AUC	95% CI
Full model	0.88	0.87–0.89	0.85	0.77–0.92
Restricted model			0.84	0.77–0.92
Clinical model			0.77	0.66–0.87
L-TRiP(cast) score			0.76	0.66–0.86

Restricted and Clinical Models

The AUC of our restricted model in plaster cast patients reached a maximum of 0.84 (95% CI 0.77–0.92) (Table 3). The restricted model comprised 11 predictor variables: age, sex, plaster cast and location, BMI, non-O blood type, current use of oral contraceptives, factor VIII activity, surgery within the past 3 months, prothrombin mutation, family history of VTE (first-degree relative), and bedridden within the past 3 months (see Table 2). Fig. 2 shows the AUC value after each addition of a predictor

into the restricted model. The clinical model consisted of 14 environmental predictor variables (see Table 2). In plaster cast patients, this model reached an AUC of 0.77 (95% CI 0.66–0.87) (Table 3).

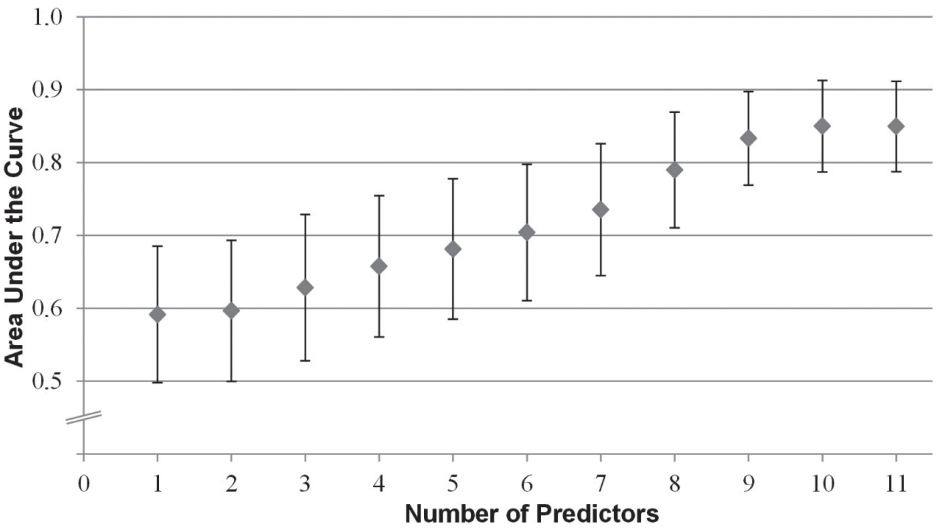

Figure 2. *AUC value after addition of each predictor into the restricted model.*
Vertical bars represent 95% CIs. Predictors: (1) age, (2) sex, (3) plaster cast and location, (4) prothrombin mutation, (5) current use of oral contraceptives, (6) family history of VTE (first-degree relative), (7) factor VIII activity, (8) bedridden within the past 3 months, (9) surgery within the past 3 months, (10) non-O blood type, (11) BMI.

L-TRiP(cast) Score

Based on the regression coefficients in the clinical logistic regression model, the L-TRiP(cast) score was developed (Table 4). For instance, a 40-y-old male who was admitted into the hospital within the past 3 months receives 5 points (including 2 points for being older than 35 y and 1 point for male sex). If this person also has rheumatoid arthritis (1 point) and a plaster cast of the lower leg (4 points), this results in a total of 10 points. In our plaster cast population, the score ranged between 4 and 20 points (out of a maximum of 29 points for men and 35 points for women). In all, 59.6% (n = 137) of the plaster cast patients had a score of at least 10 points. Fig. 3 shows the distribution of individual L-TRiP(cast) scores among cases and controls.

In the plaster cast patients, the L-TRiP(cast) score had an AUC of 0.76 (95% CI 0.66–0.86). Using a cutoff point of 10 points (59.6% of patients) to stratify individuals into high versus low risk categories, the sensitivity was 65.1%, and the specificity was 72.2%. Assuming an incidence of VTE of 2.5%, the positive predictive value of the test was 5.7%, and the negative predictive value was 98.8%. Table 5 shows predictive values that were calculated for different cutoff points.

Table 4. *L-TRiP(cast) score based on the clinical risk prediction model.*

Environmental Predictor Variable	Point Value
Age ≥ 35 and < 55 y	2
Age ≥ 55 y	3
Male sex	1
Current use of oral contraceptives	4
Cancer within the past 5 y	3
Pregnancy or puerperium	3
BMI ≥ 25 and < 35 kg/m2	1
BMI ≥ 35 kg/m2	2
Pneumonia	3
Family history of VTE (first-degree relative)	2
Comorbidity (rheumatoid arthritis, chronic kidney disease, COPD, multiple sclerosis)	1
Hospital admission within the past 3 mo	2
Bedridden within the past 3 mo	2
Surgery within the past 3 mo	2
Superficial vein thrombosis	3
Plaster cast: complete leg	5
Plaster cast: circular knee cast (ankle free)	2
Plaster cast: foot	2
Plaster cast: lower leg	4

This L-TRiP(cast) score was derived from the regression coefficients (betas) of the clinical prediction model: 0.20 < beta ≤ 0.75, 1 point; 0.75 < beta ≤ 1.25, 2 points; 1.25 < beta ≤ 1.75, 3 points; 1.75 < beta ≤ 2.25, 4 points; beta > 2.25, 5 points

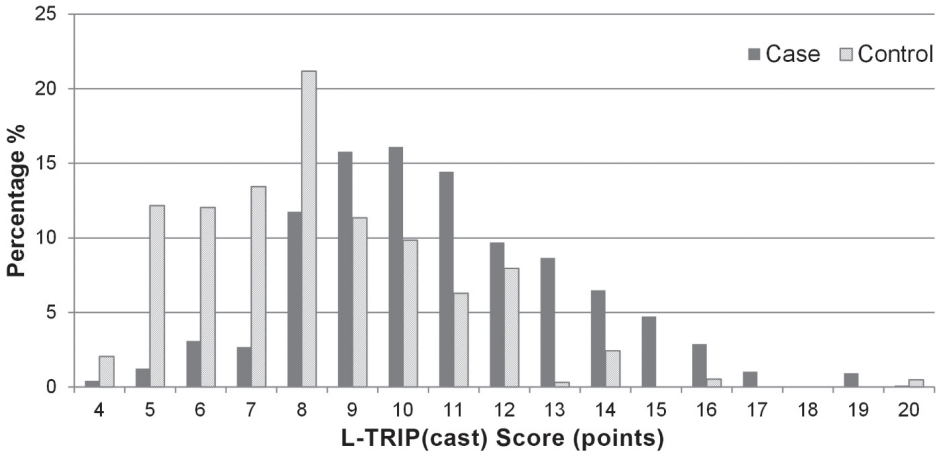

Fig. *3. Distribution of individual L-TRiP(cast) scores in the plaster cast subgroup derived from the MEGA study.*

Table 5. *Predictive performance of the L-TRiP(cast) score in plaster cast patients.*

Cutoff Point	Percent Positive	Sensitivity	Specificity	Sensitivity + Specificity	Positive Predictive Value*	Negative Predictive Value*	Likelihood Positive	Likelihood Negative
2	100.0%	100.0%	0.0%	100.0%	2.5%	99.2%	1.0	0.3
3	100.0%	100.0%	0.1%	100.0%	2.5%	99.2%	1.0	0.3
4	99.9%	100.0%	0.1%	100.0%	2.5%	98.6%	1.0	0.5
5	99.3%	99.6%	2.0%	101.6%	2.5%	99.5%	1.0	0.2
6	96.5%	98.4%	14.2%	112.6%	2.9%	99.7%	1.1	0.1
7	92.1%	95.3%	26.2%	121.5%	3.2%	99.5%	1.3	0.2
8	87.8%	92.6%	39.7%	132.2%	3.8%	99.5%	1.5	0.2
9	74.7%	80.8%	60.8%	141.7%	5.0%	99.2%	2.1	0.3
10	59.6%	65.1%	72.2%	137.2%	5.7%	98.8%	2.3	0.5
11	44.4%	49.0%	82.0%	131.0%	6.5%	98.4%	2.7	1.0
12	31.2%	34.5%	88.3%	122.9%	7.1%	98.1%	3.0	0.7
13	21.7%	24.8%	96.3%	121.1%	14.7%	98.0%	6.7	0.8
14	14.3%	16.2%	96.6%	112.8%	10.9%	97.8%	4.7	0.9

**Presuming a prevalence of VTE in plaster cast patients of 2.5%.*

Validation Cohorts

The characteristics of the THE-VTE study population, with 784 cases and 523 controls in our analyses, were similar to those of our derivation cohort. DVT was found in 460 (59%) cases, and PE (with or without DVT) in 325 (41%) cases. Plaster cast of the lower extremity was present in 32 (4.1%) cases and seven (1.3%) controls. In the Milan study, plaster cast of the lower extremity was seen in 143 (8.1%) cases and eight (0.4%) controls.

As discussed above, when selecting predictors for our restricted model, we selected variables based on availability in the validation cohorts without reducing the AUC performance. Because the MILAN study lacked data on Von Willebrand factor levels, monocyte percentage, varicose veins, and hospital admission within the past 3 months (which were strong predictors in the derivation cohort), we adjusted our restricted model. These predictors were replaced with BMI, prothrombin mutation, non-O blood type, and bedridden within the past 3 mo. The predictive AUC value of this adjusted restricted model performed similarly to the unadjusted model in the MEGA study population. Therefore, we chose to continue using these predictors in our restricted model.

Results of the validation of the different prediction scores can be found in Table 6. The clinical model showed an AUC of 0.75 (95% CI 0.55–0.94) in plaster cast patients in the THE-VTE cohort. In the Milan study population, AUCs were 0.93 (95% CI 0.86–1.00), 0.92 (95% CI 0.87–0.98), and 0.96 (95% CI 0.92–0.99) for the full, restricted, and clinical models, respectively, in plaster cast patients. The L-TRiP(cast) score performed very well, with AUCs of 0.95 (95% CI 0.91–0.99) and 0.77 (95% CI 0.58–0.96) in the Milan study and the THE-VTE study, respectively.

Table 6. *Validation results in plaster cast patients.*

	AUC (95% CI)	
Model or Prediction Score	**THE-VTE Study**	**Milan Study**
Full model	—	0.93 (0.86–1.00)
Restricted model	—	0.92 (0.87–0.98)
Clinical model	0.75 (0.55–0.94)	0.96 (0.92–0.99)
L-TRiP(cast) score	0.77 (0.58–0.96)	0.95 (0.91–0.99)

Discussion

Summary of Key Findings

In this study we developed a prediction model for the occurrence of VTE in patients with plaster cast immobilization of the lower extremity. Due to the wide range of incidence rates that have been reported and a considerable bleeding risk secondary to anticoagulant prophylaxis, current guidelines on thromboprophylaxis are contradictory. A prediction model could help clinicians decide whether or not to prescribe thromboprophylaxis in individual patients.[24,25]

The full model performed best in our derivation cohort, with an AUC of 0.85 (95% CI 0.77–0.92), and consisted of a mix of environmental risk factors, genetic risk factors, and biomarkers. However, as measurement of biomarkers and SNPs can be difficult, expensive, or take some time in clinical practice, we also developed two reduced versions of this full model: a restricted model and a clinical model. These models are more practical for clinical use and still showed good predictive characteristics, with an AUC of 0.84 (95% CI 0.77–0.92) and 0.77 (95% CI 0.66–0.87) for the restricted model (only one biomarker and two SNPs included) and the clinical model (no biomarkers or SNPs), respectively. In validation studies, the clinical and restricted models performed well in two validation populations. Of all the models, the clinical model performed best, with an AUC of 0.75 (95% CI 0.55–0.94) and 0.96 (95% CI 0.92–0.99) in the THE-VTE study and the Milan study, respectively.

Previous Prediction Models

Whereas other studies have examined risk factors and developed prediction models for thrombosis in the general population, this study focused particularly on the development of VTE in plaster cast patients. Considering the low risk of a first event

and the heterogeneous etiology of VTE, it is not efficient to develop a prediction model for the general population. Instead, targeting a specific high risk group is much more likely to lead to a model that can be used in clinical practice to distinguish individuals in whom the expected risk is sufficiently high to warrant thromboprophylactic therapy.[1] For instance, location of the plaster cast (complete leg, lower leg, etc.) was the most important predictive variable in our target group, giving specific information for these patients.

The predictive value of genetic and environmental risk factors for VTE has been described in previous studies.[3,4,26] Hippisley-Cox and Coupland reported an increased risk of VTE in the general population in association with overweight, COPD, varicose veins, congestive heart failure, chronic renal disease, cancer, inflammatory bowel disease, hospital admission within the past 6 months, use of antipsychotic drugs, use of oral contraceptives, use of hormone replacement therapy, use of tamoxifen, and smoking, which resulted in an AUC value of 0.75 (95% CI 0.74–0.76) in their validation cohort, which is in line with our results.[4] However, one very well established risk factor, i.e., immobilization, was not incorporated into this model. de Haan et al. recently found that multiple SNP testing had an additional predictive value in the prediction of VTE compared with a model with environmental variables only (also partially MEGA study data).[6] They identified five common SNPs and incorporated these variables into a prediction model for the general population, together with environmental risk factors. This model had an AUC of 0.77 (95% CI 0.74–0.80).[6]

There have been only a few studies, predominantly in cancer-induced thrombosis, that have investigated the predictive role of biomarkers, such as high factor VIII and prothrombin fragment 1 + 2, in the prediction of VTE.[7,9] While other studies have focused on environmental risk factors, genetic risk factors, or biomarkers only, we incorporated all three types of predictor variables into our model. So far, this is the only prediction model for VTE to our knowledge that has combined all of these variables and that has focused on plaster cast patients.

Limitations of the Study

Although we incorporated genetic risk factors, environmental risk factors, and biomarkers in our model, we were not able to include age and sex as predictor variables at first, since the controls in our study were frequency matched on age and sex. To

overcome this, control individuals were weighted to the age and sex distribution of the Dutch population, which made it possible to estimate the real effect of age and sex on the risk of VTE in our case–control study. We performed a sensitivity analysis with and without weighting of control individuals: the results for the weighted analyses were equal to those of the unweighted analyses in both the derivation and validation studies. This way, age and sex were incorporated into our models as predictor variables, making our risk score suitable for patients from 18 up to 70 y old. Another limitation of the study was that blood collection was performed after the occurrence of thrombosis. As a result, the levels of coagulation factors may have been a consequence of the thrombosis rather than a cause. However, increased levels of factor VIII and fibrinogen measured after the occurrence of thrombosis have been shown not to be due to acute phase reactions.[27] In fact, high factor VIII levels seem to be a permanent phenomenon, and repeated measurements of factor VIII show little variation.[28,29] A third limitation was that general information on anticoagulation therapy was available, but information on possible thromboprophylaxis during plaster cast was missing. Nonetheless, if we look at the results of a survey on thromboprophylaxis conducted in the Netherlands in 2002, which overlaps with the inclusion period of our study, 30% of orthopedic surgeons provided thromboprophylaxis during lower leg plaster cast, and 88% during complete leg plaster cast.[30] Therefore, VTE risk may have been underestimated in this study. A fourth limitation of the study is that the relatively small number of individuals with plaster cast (n = 230) hinders development of a prediction model specifically targeted to this group. To overcome this issue and avoid overfitting, we first developed our model in the entire MEGA study population and then tested our full model in the plaster cast subgroup. Finally, using a c-statistic alone for building a prediction model may eliminate important risk factors. To overcome this, we first developed our full model based on clinical as well as statistical criteria. Candidate predictors were retained based on (1) a forward selection procedure or (2) well-established association in the literature. We used the c-statistic only to slim down our full model so that the same predictive power could be reached with fewer predictor variables.

Clinical Implications

Our study showed a good performance of the different prediction models in plaster cast patients. Although we found an added value of genetic variance and biomarker information in the prediction of VTE, the clinical model (with environmental factors only) performed only slightly less well than the full model, with a good discriminative statistic

of 0.77 (95% CI 0.66–0.87) in the derivation data. Moreover, in our validation sets, the clinical model performed as well or even better than the full model, with an AUC of 0.75 (95% CI 0.55–0.94) and 0.96 (95% CI 0.92–0.99) in the THE-VTE study and the Milan study, respectively. Therefore, it is doubtful whether information on genetic variance and biomarkers will lead to higher accuracy in the prediction algorithm. In addition, genetic testing is currently not practical in the clinical setting and probably less cost-effective (due to the small prevalence of some genetic variants), and therefore the diagnostic value of these predictors might be limited.

Currently, the American College of Chest Physicians advises that pharmacologic thromboprophylaxis not be used in patients with isolated lower leg injuries requiring leg immobilization.[12] The UK National Institute for Health Care and Excellence guidelines recommend considering VTE prophylaxis after evaluating the risks and benefits in clinical discussion with the patient.[31] In addition, the British Society for Haematology recommends prophylaxis for patients at high risk of VTE associated with lower limb plaster cast.[32] Our L-TRiP(cast) score, based on the clinical model, classifies individuals with plaster cast of the lower extremity as high risk or low risk for VTE. This may give guidance to clinicians on prescribing thromboprophylaxis, in line with the latest guidelines. Defining a definite cutoff point is not straightforward. We cautiously suggest using a cutoff point of 9 points to classify individuals as being at high risk for VTE, in which case 74.7% of the people with plaster cast (cases and controls) in our study were identified as high risk. In this way, our risk score can identify a large proportion of people at risk; assuming an overall incidence of VTE of 2.5% (or more with increasing age), the model in these patients has a positive predictive value for the development of VTE of 5.0% while only 0.8% of individuals who scored lower than 9 points will develop VTE. For recurrence, a ≥5.0% risk is considered as an indication for thromboprophylaxis[33], which outweighs the risk of major bleeding. For short term treatment (6 weeks for plaster cast), the bleeding risk is obviously much lower and is estimated at 0.5%. Furthermore, a higher sensitivity could be preferred over a higher specificity, as the burden of missing a VTE might be worse than the burden of overtreatment (i.e., prophylaxis without therapeutic consequences and bleeding complications). While an established cutoff is lacking, clinicians may determine the trade-off between thrombosis and bleeding risk using this decision rule, until additional results from other studies are available (ideally, a randomized controlled trial that compares thromboprophylaxis in

all plaster cast patients, or never thromboprophylaxis, with the decision rule based on our L-TRiP[cast] score).

Conclusion

By using information on environmental risk factors, genetic risk factors, and biomarkers, we were able to develop models that predict the risk of VTE after cast immobilization of the lower extremity. The derivation models in this study show that determination of biomarkers and genetic variance leads to better accuracy in the prediction of VTE in plaster cast patients. However, the validation data show that the clinical model performs as well, or even better. The L-TRiP(cast) score may therefore be more efficient and can be used in the clinical setting. These results can give guidance in clinical decision-making until an unambiguous guideline for thromboprophylaxis therapy in these patients is available, so that not every patient needs to be exposed to the risk and burden of anticoagulant treatment.

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Supplement material

Analysis plan for the development of the L-TriP(cast) score

The MEGA study is a case-control study, set up to assess the risk of venous thrombosis for several risk factors (including interaction between risk factors). Common (acquired) risk factors, biomarkers and genetic risk factors were measured through questionnaires and blood sampling. Causal relationships were estimated by calculating relative risks (by means of the odds ratio). Cases were identified from six anticoagulation clinics in the Netherlands and initially control subjects were partners of cases. Because not all cases had a partner or some partners refused to cooperate, it was decided to include extra controls, who were identified using a random digit dialing method.

In the past years many risk factors have been identified using the MEGA data. This information and that of other studies has led to current knowledge on dozens of risk factors for venous thrombosis. Combining these risk factors now allows identifying patients at high risk of developing venous thrombosis, in certain situations. Hence, in recent years, the focus of the MEGA-study has shifted from identifying separate risk factors towards prediction of thrombosis, i.e. identification of high-risk groups. This development is a logical and direct result of the knowledge that was gained during the past years.

The main goal of the current project was to develop a prediction model for venous thrombosis for patients with plaster cast of the lower extremity. The MEGA database was the ideal source of information for this study (case-control database with all information on biomarkers, acquired and genetic risk factors for venous thrombosis). As planned, we developed a multivariate logistic regression model to identify predictors. Risk factor selection was based both on clinical importance and the strength of the causal relationship. (This analysis has been described in detail in the manuscript itself). A validation study performed in two databases was added in a later stage to demonstrate its external validity for the general population (and to show that results were not just data-driven). During the review process it was decided to weigh all controls subjects to the age and sex distribution of the Netherlands in 2001, which was necessary due to the age- and (opposite) sex-matching. This way, age and sex could be incorporated as predictors in de model (which improved the clinical usefulness of the L-TRiP(cast) score).

Missing data and multiple imputation

Multiple imputation was used to complete missing predictor values. Data on environmental risk factors was collected by means of a questionnaire, missing data on the questionnaire resulted in this missing data. Blood collection was terminated for logistic reasons on May 31, 2002. For participants included after this date no blood was sampled which resulted in missing data which is quite likely completely at random. For patients included after May 31, 2002, buccal swabs were collected for DNA analyses. Patients who did not return their buccal swab had missing data for the DNA variables.

Detailed information on laboratory analyses.

Coagulation markers such as prothrombin (factor II [FII]) activity, factor VII (FVII) activity, factor VIII (FVIII) activity, antithrombin (AT) activity, protein C (PC) activity and protein S (PS) antigen level were 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 factor IX antigen (FIX) were determined by enzyme-linked immunosorbent assay (ELISA). Fibrinogen activity was measured on the STA-R analyzer according to methods of Clauss. In the presence of excess thrombin, the coagulation time of a diluted plasma sample was measured. 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). Hemorheological markers such as hematocrit, white blood cell count (WBCC), percentage/number lymphocytes, percentages/number monocytes, percentage/number granulocytes, red blood cell count (RBCC), hemoglobin level, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), red cell distribution width (RDW), total homocysteine, total cysteine, methionine and factor X antigen level were measured using the Beckman coulter analyzer.

Table. *Basic characteristics of cases and controls of the derivation cohort*

Acquired predictor variables	Cases		Controls	
	No.	%	No.**	%
All	4446		6118	
Age				
0-34	819	20,1%	1306	21,3%
35-54	2037	47,0%	2931	47,9%
55-70	1590	35,8%	1881	30,7%
Sex				
Female	2422	54,5%	3284	53,7%
Male	2024	45,5%	2834	46,3%
Body Mass Index (BMI)				
0-25	1723	38,8%	3057	50,0%
26-30	1820	40,9%	2242	36,6%
31-35	663	14,9%	649	10,6%
>35	240	5,4%	170	2,8%
Smoking				
never	1494	33,6%	2439	39,9%
former	1355	30,5%	1722	28,1%
current	1597	35,9%	1957	32,0%
Varicose veins	1433	32,2%	1180	19,3%
Cancer within the past 5 years	424	9,5%	112	1,8%
Congestive heart failure	68	1,5%	50	0,8%
Comorbidity *	539	12,1%	380	6,2%
Rheumatoid arthritis	147	3,3%	138	2,3%
Chronic kidney disease	60	1,3%	26	0,4%
Chronic Obstructive Pulmonary Disease (COPD)	297	6,7%	198	3,2%
Multiple Sclerosis (MS)	35	0,8%	18	0,3%
Cardiovascular disease *	532	12,0%	468	7,7%
Angina Pectoris (AP)	332	7,5%	281	4,6%
Heart attack	454	10,2%	395	6,5%

Table. *Basic characteristics of cases and controls of the derivation cohort (continued)*

Acquired predictor variables	Cases		Controls	
	No.	%	No.**	%
Cerebrovascular events *	109	2,5%	95	1,6%
Stroke	45	1,0%	35	0,6%
Transient Ischemic Attack (TIA)	64	1,4%	60	1,0%
Claudication	421	9,5%	396	6,5%
Family history of VTE (first-degree)				
1 family member	1271	28,6%	1007	16,5%
>1 family member	361	8,1%	207	3,4%
Hospital admission within the past 3 months	793	17,8%	164	2,7%
Bedridden within the past 3 months	573	12,9%	230	3,8%
Paralysis (partial)	51	1,1%	16	0,3%
Surgery within the past 3 months	742	16,7%	170	2,8%
Pregnancy or puerperium	170	3,8%	89	1,5%
Current use of antipsychotic medication	45	1,0%	21	0,3%
Current use of tamoxifen	21	0,5%	3	0,0%
Current use of hormonal replacement therapy	128	2,9%	165	2,7%
Current use of oral contraceptives	763	17,2%	1184	19,4%
Superficial vein thrombosis	420	9,4%	109	1,8%
Hepatitis*	16	0,4%	8	0,1%
Hepatitis A	3	0,1%	2	0,0%
Hepatitis B	9	0,2%	4	0,1%
Hepatitis C	7	0,2%	4	0,1%
Pneumonia	305	6,9%	94	1,5%
Inflammatory disease*	1090	24,5%	1099	18,0%
Urinary tract infection / Cystitis	368	8,3%	360	5,9%
Pyelonephritis	32	0,7%	32	0,5%
Arthritis	249	5,6%	277	4,5%
Bursitis	161	3,6%	191	3,1%
Inflammation (other body parts)	472	10,6%	408	6,7%
Tropical diseases	5	0,1%	2	0,0%

Table. *Basic characteristics of cases and controls of the derivation cohort (continued)*

Acquired predictor variables	**Cases**		**Controls**	
	No.	**%**	**No.****	**%**
Plaster cast and location	194	4,4%	36	0,6%
Complete leg	49	1,1%	6	0,1%
Circular knee cast (ankle free)	3	0,1%	1	0,0%
Lower leg	130	2,9%	24	0,4%
Foot	12	0,3%	5	0,1%
Hemorheological and coagulation predictor variables	**Mean**	**SD**	**Mean**	**SD**
Factor VIII activity	138,9	44,2	111,4	39,7
von Willebrand Factor (vWF) antigen level	147,4	56,1	110,9	48,2
Factor XI activity	105,3	21,1	100,1	19,8
Percentage of monocytes	6,3	2,1	5,8	2,1
Total cysteine	236,2	50,4	225,5	50,2
Red cell Distribution With (RDW)	13,2	1,3	12,8	1,1
Genetic predictor variables	**no.**	**%**		
Prothrombin mutation				
G20210A mutation	237	5,3%	117	1,9%
Factor V Leiden mutation				
AG mutation	673	15,1%	316	5,2%
AA mutation	26	0,6%	9	0,1%
Non-O blood type				
OX type	2408	54,2%	2626	42,9%
Non-O type	593	13,3%	721	11,8%

* *Does not add up to total percentage as some patients had multiple diseases*

** *Original data, controls not weighted*

Table. *Univariate and multivariate analyses showing ORs for VTE, comparing cases and controls*

Acquired predictor variables	Univariate			Full model		
	OR*	95% CI		OR*	95% CI	
Age						
<35 years	**ref**	-	-			
≥35 years and <55 years	**2,0**	1,8	2,2	**1,6**	1,4	1,9
≥55 years	**3,2**	2,9	3,6	**2,0**	1,6	2,4
Sex - male	**0,8**	0,7	0,9	**1,9**	1,6	2,2
Body Mass Index (BMI) kg/m^2						
<25	**ref**	-	-	**ref**	-	-
≥25 and <30	**1,7**	1,5	1,8	**1,5**	1,4	1,3
≥30 and <35	**2,1**	1,9	2,4	**1,5**	1,5	1,2
≥35	**3,1**	2,5	3,9	**1,9**	1,3	2,6
Smoking						
never	**ref**	-	-	**ref**		
former	**1,6**	1,4	1,7	**1,3**	1,1	1,4
current	**1,3**	1,2	1,5	**1,5**	1,3	1,7
Varicose veins	**2,4**	2,2	2,7	**1,7**	1,5	2,1
Cancer within the past 5 years	**7,3**	5,9	9,1	**4,8**	3,6	6,5
Congestive heart failure	**2,3**	1,5	3,4	**1,7**	0,9	3,1
Comorbidity	**2,3**	1,9	2,7	**1,5**	1,1	1,9
Cerebrovascular events	**2,2**	1,6	2,9	**1,3**	0,9	2,0
Family history of VTE (first-degree)	**ref**	-	-	**ref**	-	-
1 family member	**2,6**	2,3	2,9	**1,9**	1,7	2,2
>1 family member	**3,8**	1,5	9,5	**3,1**	1,0	9,4
Hospital admission within the past 3 months	**8,1**	6,7	9,9	**3,6**	2,7	4,7
Bedridden within the past 3 months	**3,3**	2,8	4,0	**2,4**	1,8	3,0
Paralysis (partial)	**5,4**	2,9	9,9	**3,3**	1,4	7,8
Surgery within the past 3 months	**7,2**	5,9	8,7	**3,5**	2,7	4,6
Pregnancy or puerperium	**2,2**	1,7	2,9	**6,1**	4,0	9,5
Current use of antipsychotic medication	**3,5**	2,0	5,9	**2,9**	1,5	5,7
Current use of tamoxifen	**11,6**	3,3	41,2	**1,6**	0,4	6,0

Table. *Univariate and multivariate analyses showing ORs for VTE, comparing cases and controls (continued)*

Acquired predictor variables	Univariate			Full model		
	OR*	95% CI		OR*	95% CI	
Current use of hormonal replacement therapy	**1,5**	1,2	2,0	**1,5**	1,1	2,2
Current use of oral contraceptives	**2,0**	1,8	2,3	**7,3**	6,0	8,8
Superficial vein thrombosis	**7,3**	5,8	9,3	**3,6**	2,6	4,9
Hepatitis	**3,5**	1,3	9,3	**4,5**	0,9	23,5
Pneumonia	**4,8**	3,6	6,3	**3,4**	2,3	4,9
Plaster cast and location						
No plaster (in lower extremities)	**ref**	-	-	**ref**	-	-
Complete leg	**10,7**	4,3	26,6	**11,1**	4,0	30,8
Circular knee cast (ankle free)	**3,7**	0,4	35,8	**1,8**	0,2	19,0
Lower leg	**8,7**	5,5	13,7	**9,6**	5,3	17,6
Foot	**4,0**	1,4	11,5	**1,5**	0,3	7,4
Hemorheological and coagulation predictor variables	**OR***	**95% CI**		**OR**	**95% CI**	
Factor VIII activity (%), 100%=1 IU/ml						
<92	**ref**	-	-	**ref**	-	-
>=92 <126	**2,2**	1,8	2,6	**1,6**	1,2	2,3
>=126	**5,5**	4,5	6,8	**2,9**	1,8	4,6
von Willebrand Factor (vWF) antigen level (%)						
<89	**ref**	-	-	**ref**		
>=89 <126	**2,2**	1,8	2,6	**1,6**	1,2	2,3
>=126	**6,2**	5,4	7,1	**3,2**	2,2	4,6
Factor XI activity (%), 100%=1 IU/ml						
<91	**ref**	-	-	**ref**		
>=91 <108	**1,3**	1,1	1,5	**1,1**	0,9	1,3
>=108	**2,0**	1,7	2,4	**1,4**	1,1	1,8
Percentage of monocytes (%)						
<4,9	**ref**	-	-	**ref**		
>=4,9 <6,7	**1,3**	1,1	1,4	**1,5**	1,2	1,7
>=6,7	**1,5**	1,3	1,8	**1,9**	1,5	2,4

Table. *Univariate and multivariate analyses showing ORs for VTE, comparing cases and controls (continued)*

Acquired predictor variables	Univariate			Full model		
	OR*	95% CI		OR*	95% CI	
Total cysteine (μM)						
<0,29	**ref**	-	-	**ref**		
>=0,29 <0,40	**1,5**	1,3	1,7	**1,4**	1,1	1,7
>=0,40	**2,0**	1,8	2,2	**1,4**	1,2	1,8
Red cell Distribution With (RDW) (%)						
<12,3	**ref**	-	-	**ref**		
>=12,3 <13,1	**1,4**	1,2	1,6	**1,3**	1,1	1,6
>=13,1	**2,3**	1,9	2,8	**2,0**	1,6	2,4
Genetic predictor variables	**OR***	**95% CI**		**OR**	**95% CI**	
Prothrombin mutation						
G20210A mutation	**2,7**	2,0	3,7	**2,8**	2,1	3,7
Factor V Leiden mutation						
GG	**ref**	-	-	**ref**		
AG mutation	**3,2**	2,6	3,9	**3,2**	2,6	4,0
AA mutation	**4,0**	1,0	15,4	**5,7**	1,6	19,7
Non-O blood type						
O type	**ref**	-	-	**ref**		
OX type	**2,0**	0,8	5,0	**1,4**	0,5	4,3
Non-O type	**2,7**	1,4	5,4	**1,9**	0,8	4,3

**Weighted analyses*


CHAPTER

Venous thrombosis risk after arthroscopy of the knee: derivation and validation of the L-TRiP(ascopy) score

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Abstract

Background

Patients at high risk for Venous Thrombosis (VT) following knee arthroscopy could potentially benefit from thromboprophylaxis. We explored the predictive values of environmental, genetic risk factors and levels of coagulation markers to integrate these into a prediction model.

Methods

Using a population-based case-control study into the etiology of VT we developed a *Complete* (all variables), *Screening* (easy to use in clinical practice) and *Clinical* (only environmental risk factors) model. The *Clinical* model was transformed into the *L-TRiP(ascopy)* score. Model validation was performed both internally and externally in another case-control study.

Results

4943 cases and 6294 controls were maintained in the analyses, 107 cases and 26 controls had undergone knee arthroscopy. Twelve predictor variables (8 environmental, 3 hemorheological and 1 genetic) were selected from 52 candidates and incorporated into the *Complete* model (Area Under the Curve (AUC) of 0.81, 95%CI 0.76–0.86). The *Screening* model (9 predictors: environmental factors plus FVIII activity) reached an AUC of 0.76 (95%CI 0.64–0.88) and the *Clinical (and corresponding L-TRiP(ascopy)* model an AUC of 0.72 (95%CI 0.60 – 0.83). In the internal and external validation, the *Complete* model reached an AUC of 0.78 (95%CI 0.52–0.98) and 0.75 (95%CI 0.42-1.00), respectively, while the other models performed slightly less well.

Conclusions

These results show that environmental risk factors, coagulation factors, and genetic determinants in patients can be used for prediction of VT risk in patients who undergo arthroscopy of the knee. These results can be used to identify those individuals at high risk of developing VT and provide selective and possibly stronger VT prevention to these patients.

Introduction

In general, orthopedic surgery is associated with a high risk of venous thrombosis (VT), the composite of deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] This can be understood when we consider the long duration of surgery, the extensive tissue damage during hip or knee replacement and the associated immobilization. For general knee arthroscopy this is different: hardly any tissue damage occurs and the duration of the procedure is short (15-20 min). However, the risk of VT following arthroscopy of the knee is not negligible, with symptomatic incidence rates varying around 1%.[2-6] Knee arthroscopy is the most commonly performed orthopedic procedure with worldwide 4 million arthroscopies carried out yearly.[7] Therefore, this will lead to high absolute numbers of, theoretically preventable, VT cases (40 000 VTs annually assuming a risk of 1%). In addition, numerous fatal cases after surgery have been described[8, 9], as can be expected based on a 30-day VT fatality rate of 3.0%.[10] Hence, on estimation 1 200 patients die yearly within 30 days after knee arthroscopy worldwide. Moreover, long term complications such as post-thrombotic syndrome affect about 40% of thrombosis patients.[11] Therefore the impact of VT is considerable, even in this generally young and healthy patient population.

Several studies have been performed to obtain more insight in the development of VT after arthroscopic knee surgery. Recently, we showed in the POT-KAST trial, a large Randomized Controlled Trial (1 451 patients) comparing Low Molecular Weight Heparin with no treatment, that there is no effectiveness for thromboprophylaxis following knee arthroscopic surgery, as the risk of VT was equal (~ 0.6%) in the treated and untreated group.[12]

Multiple high risk groups appear to exist: It was recently described that hospital admission before surgery was predictive of thrombosis (Hazard Ratio 14.1, 95% CI: 5.3–37.6).[3] Another study showed that patients undergoing anterior cruciate ligament (ACL) reconstruction had a higher VT risk compared with patients undergoing less invasive arthroscopic procedures.[13] Other risk factors, such as a history of malignancy[2], a history of VT[14], use oral contraceptives, being overweight or having a genetic predisposition (Factor V Leiden, non-O blood type, prothrombin 20210A mutation) have also been identified to elevate postoperative risk.[2, 15] Hence, it should theoretically be possible to distinguish between high or low risk of VT after knee arthroscopy by combining all information into one prediction model, instead of measuring single risk

factor associations. If these groups can be targeted, the considerable morbidity and mortality due to VT after this procedure may yet be preventable.

The aim of this study was to investigate the combined predictive value of environmental and genetic risk factors, biomarkers and levels of coagulation markers on the development of VT in knee arthroscopy patients. We aimed to develop a prediction model to assist clinicians to decide whether or not to prescribe thromboprophylaxis in individual patients.

Methods

Study design

For model development, data from a large population-based case-control study, the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA study) were used. Details of this study have been published previously.[16] In short, between 1999 and 2004, all consecutive patients aged 18 to 70 years with a first deep vein thrombosis, pulmonary embolism or both were recruited from six anticoagulation clinics in the Netherlands (n=4 956). The control-group (n=6 297) consisted of partners of participating patients and of other controls who were frequency matched with respect to sex and age and identified using a random digit dialing method. Approval for this study was obtained from the Medical Ethics Committee of the Leiden University Medical Center and all participants provided written informed consent.

Data collection and laboratory analysis

All participants completed a questionnaire, including potential risk factors for VT such as orthopedic surgery, current use of medication and co-morbidity in the year before the venous thrombotic event. A blood sample was collected approximately three months after discontinuation of oral anticoagulant therapy for patients and controls included from the start of the study until May 31, 2002. Detailed information on laboratory analyses from coagulation and hemorheological and other markers can be found in the supplement material. In patients who were still on anticoagulant therapy one year after the event, blood was drawn during treatment. After June 1, 2002 and for participants who were unable to visit the clinic, DNA was collected by means of buccal swabs sent by mail. Factor V Leiden (F5, rs6025), prothrombin G20210A (F2, rs1799963) mutation and ABO-blood group were determined.

Model Derivation

The prediction model was developed using the data from the MEGA study population. Subjects with multiple orthopedic surgeries or other operations in combination with a knee arthroscopy were excluded from analyses. To incorporate age and sex as predictor variables (because controls were frequency matched on age and sex) we weighted control subjects (for age and sex) to the age and sex distribution of the Dutch population in 2001 (Statistics Netherlands). Missing values were imputed (we imputed 5 datasets by multiple imputation and results were pooled according to Rubin's rules). Vitamin K dependent coagulation factors from patients who were still on anticoagulation treatment during blood collection were set as missing values and imputed as well. In the supplement material detailed information on missing data for risk factors incorporated in the prediction model is provided.

We aimed to develop three models; a *Complete* model (all variables and highest discriminative ability), a *Screening* model (including a minimum number of all types of predictors with maximum discriminative performance to improve clinical usefulness) and a *Clinical* model (only environmental risk factors). Development of all models was based on a method we described in a previous study, using a multivariate logistic regression approach.[17] In short, candidate predictors were identified in the whole MEGA study population (n=11 237) (*step 1 and 2*) (Fig 1). Candidate predictors (already derived from our previous study) were entered in the *Complete* prediction model by hand, and a univariate logistic regression was conducted for all candidate predictors in the entire MEGA group (*step 3*). We started fitting our *Complete* model with the strongest predictor (based on highest Area Under the Curve [AUC] in the arthroscopy subgroup) (n=133). Further predictor selection was based on the variable that resulted in the strongest increase in AUC, in the knee arthroscopy subgroup (*step 4*) (addition of predictors was stopped when AUC increase was less than 0.01 points). Age and sex were forced in *all* models based on clinical importance. For calculating the AUC, a Receiver Operating Characteristic (ROC) was constructed. Model overfitting was prevented by conducting a ROC analysis in the arthroscopy subgroup only (using the beta coefficient derived from the logistic regression model calculated in the entire MEGA study population [n=11 237]) instead of conducting a regression in the small arthroscopy subgroup. Next to a *Complete* model, a *Screening* model was developed in a similar way (*step 5*). Finally, we developed a *Clinical* model using environmental risk factors only (*step 6*).

Risk Score

We developed a Risk Score, the Leiden-Thrombosis Risk Prediction(arthroscopy) score, [*L-TRiP(ascopy) score*] for VT risk following knee arthroscopy that was based on the beta coefficients for predictor variables in the *Clinical* model (using the following rule: if Beta was >0.25 and ≤0.75, this yielded 1 point, for; Beta>0.75 and ≤1.25=2 points; Beta>1.25 and ≤1.75=3 points; Beta>1.75 and ≤2.25=4 points; Beta>2.25 and ≤2.75=5 points; Beta>2.75=6 points). The *L-TRiP(ascopy) score* was the sum of these points. Assuming two overall prevalences of either 0.5% or 1.5% for VT in patients who undergo knee arthroscopy, we calculated sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and the negative likelihood ratio for different cut off points of the *L-TRiP(ascopy) score*.

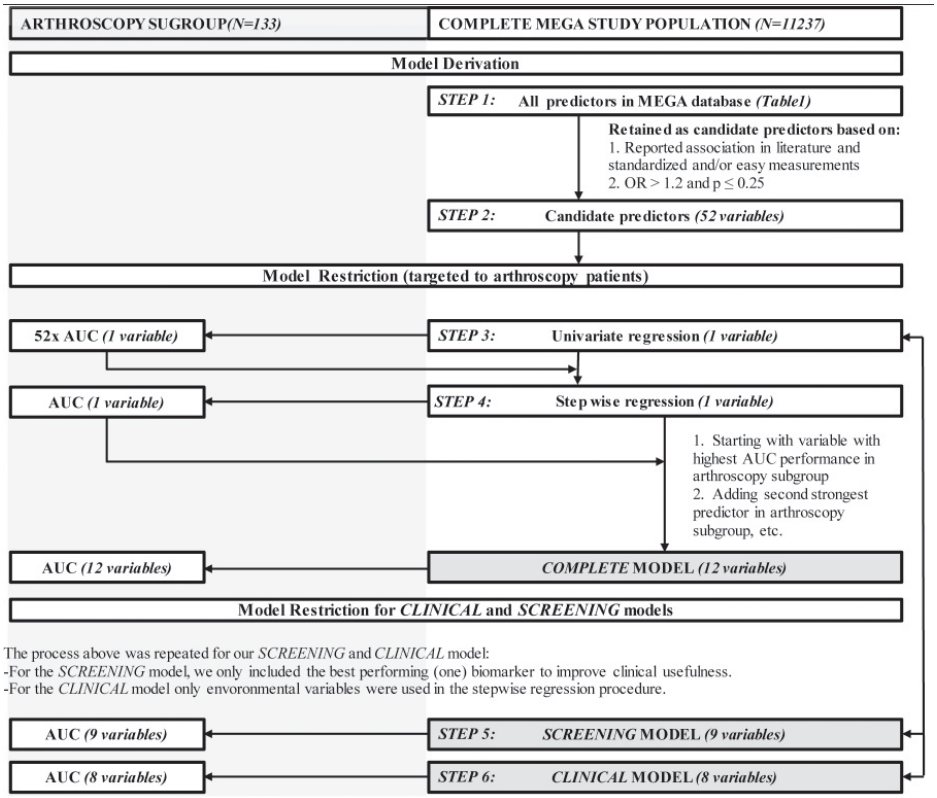

Figure 1: *Flow-chart of the derivation process for development of the L-TRiP(ascopy) score.*

Model validation

A bootstrapping procedure was performed to internally validate our results. Using the imputed dataset, we resampled our arthroscopy subgroup (1000 replications with replacement), after which all models were validated in this new population. In addition, THE VTE case-control study into the etiology of VTE, which contains 784 cases and 523 controls (Leiden/Cambridge) was used for external validation of the *L-TRiP(ascopy)* score. Details of this study have been published previously.[18] For each subject in THE VTE study, prognostic scores were calculated using regression coefficients from the prediction models derived from the MEGA study. All analyses were performed in IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. The weighted analyses were performed in Stata SE, version 14.

Results

Study population

4 943 cases and 6 294 controls were maintained in the analyses after exclusion of 13 participants who underwent multiple orthopedic operations after the arthroscopy. Among all cases 2 881 (58%) had a DVT, 1618 (33%) a PE and 444 (9%) both. 107 cases and 26 controls had undergone knee arthroscopy within one year before thrombosis or index date, respectively (of whom most patients (~75%) within 3-months)[19]. Thirteen of them (10%) underwent ligament reconstruction from the anterior cruciate ligament and/or posterior cruciate ligament. Compared with the complete MEGA study population, subjects who underwent knee arthroscopy were slightly younger (mean 44.6 years vs 47.7 years), and more often male (58% vs 46%).

Model derivation

52 candidate predictors were identified in the MEGA study population (Table 1). Strong predictors in both the total MEGA study population and arthroscopy subgroup were: family history of venous thrombosis, current use of oral contraceptives and having been bedridden within the past 3 months. Persons who underwent knee arthroscopy without ligament reconstruction had a 5-fold increased risk of developing VT, odds ratio (OR) 5.1, 95% confidence interval (95%CI 3.3 – 8.0), while those who had cruciate ligament reconstruction had an 18-fold increased risk (OR 17.5 [95%CI 2.3 – 134.8]), compared with subjects who did not have surgery.

Complete model

Twelve predictor variables (8 environmental risk factors, 3 hemorheological factors and 1 genetic marker) were incorporated into the Complete prediction model. Risk factors included in the model were: age, sex, Von Willebrand Factor (vWF) activity, family history of VT, Factor V Leiden mutation (FV Leiden), having been bedridden within the past 3 months, current use of oral contraceptives, (type) of knee arthroscopy, Factor VIII (FVIII) activity, presence of varicose veins, monocyte percentage and having congestive heart failure. This combination of risk factors resulted in an AUC of 0.81 (95%CI 0.70 – 0.93) (Table 2). Fig 2 shows the AUC values of our Complete model after step-wise addition of these predictor variables.

Table 1. *Candidate predictor variables*

Environmental predictor variables	
Age	Hospital admission within the past 3 months
Sex	Bedridden within the past 3 months
Smoking	Paralysis (partial)
Varicose veins	Surgery within the past 3 months
Cancer within the past 5 years	Current Pregnancy or puerperium
Congestive heart failure	Current use of antipsychotic medication
Comorbidity	Current use of tamoxifen
- Rheumatoid arthritis	Current use of hormonal replacement therapy
- Chronic kidney disease	Current use of oral contraceptives
- Chronic Obstructive Pulmonary Disease (COPD)	Thrombophlebitis
- Multiple Sclerosis (MS)	Hepatitis
Cardiovascular events	Pneumonia
- Angina Pectoris (AP)	Inflammation
- Heart attack	- Urinary tract infection / Cystitis
Cerebrovascular events	- Pyelonephritis
- Stroke	- Arthritis
- Transient Ischemic Attack (TIA)	- Bursitis
Body Mass Index (BMI)	- Inflammation (other body parts)
Claudication	- Tropical diseases
Family history of VT	(Type of) Arthroscopy

Table 1. *Candidate predictor variables (continued)*

Environmental predictor variables	
Hemorheologic and coagulation predictor variables	
Fibrinogen activity	Percentage/number granulocytes
Factor VIII activity	Red Blood Cell Count (RBCC)
Von Willebrand Factor (vWF) (%)	Hemoglobin level
Factor II activity	Mean Cell Volume (MCV)
Factor VII activity	Mean Cell Hemoglobin (MCH)
Factor X antigen level	Mean Cell Hemoglobin Concentration (MCHC)
Protein C activity	Red cell Distribution With (RDW)
Factor XI activity	Antithrombin activity
Hematocrit	Total homocysteine
White Blood Cell Count (WBCC)	Total cysteine
Percentage/number lymphocytes	Methionine
Percentage/number monocytes	
Genetic predictor variables	
Factor V Leiden mutation	
Prothrombin mutation	
Non-O blood type	

Table 2. *AUC values of the Complete, Screening, Clinical model and L-TRiP(ascopy) score in the MEGA and VTE study*

MODEL	**MEGA study**			**Internal validation**			**External validation: VTE study**		
	AUC	**95% CI**		**AUC**	**95% CI**		**AUC**	**95% CI**	
Complete model	0.81	0.70	0.93	0.78	0.67	0.89	0.75	0.42	1.00
Screening model	0.76	0.64	0.88	0.71	0.59	0.83	0.73	0.40	1.00
Clinical model	0.72	0.60	0.83	0.64	0.53	0.76	0.78	0.48	1.00
L-TRiP(ascopy) score	0.73	0.63	0.84	0.67	0.54	0.80	0.77	0.43	1.00

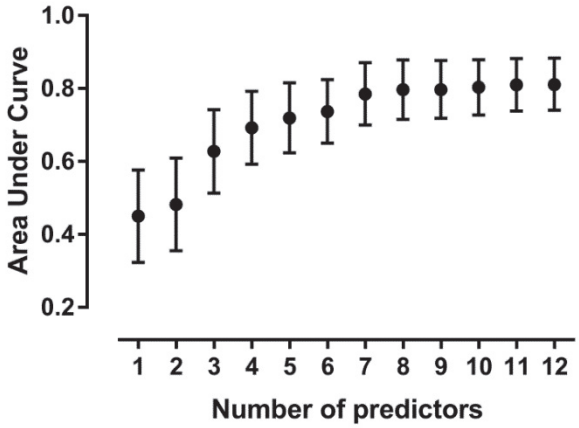

Figure 2. *AUC values of the Complete model for step-wise addition of the following predictors: age, sex, von Willebrand Factor activity, family history of VT, Factor V Leiden mutation, being bedridden within the past 3 months, current use of oral contraceptives, (type) of knee arthroscopy, Factor VIII activity, presence of varicose veins, monocyte percentage and having congestive heart failure.*

Screening model

Our Screening model consisted of nine predictors (all environmental risk factors of the Complete model plus FVIII activity) and reached an AUC of 0.76 (95%CI 0.64 – 0.88). Although vWF increased model performance more than FVIII (AUC increase of 0.02), FVIII was chosen over vWF as FVIII activity can be measured more easily in most clinics.

Clinical Model and L-TRiP(ascopy) score

The Clinical model resulted in an AUC of 0.72 (95%CI 0.60 – 0.83) and consisted of all eight environmental risk factors that were also included in the Complete and Screening model. The L-TRiP(ascopy) score (Table 3) derived from this model resulted in an AUC of 0.73 (95%CI 0.63 – 0.84). Table 4 gives an overview of discriminative values for all cut-off points from the L-TRiP(ascopy) score. For example, a cut-off value of 7 results in a sensitivity and specificity of 77.8% and 40.2% respectively, to identify patients at high risk of developing VT. Figure 3 shows the score distribution among cases and controls.

Table 3. *L-TRiP(ascopy) score*

Risk Score	Points	Original Beta
Age >= 35 and <55	2	0.78
Age >55	3	1.48
Male sex	1	0.39
Current use of oral contraceptives	3	1.43
Family history of VT (1 family member)	2	0.82
Family history of VT (>=2 family members)	3	1.47
Bedridden within the past 3 months	3	1.38
Varicose Veins	1	0.68
Congestive heart failure	1	0.49
Knee arthroscopy	4	1.76
Ligament reconstruction	6	2.93

This score was derived from the regression coefficients (Beta) of the Clinical prediction Model. Beta>0.25 and ≤0.75=1; Beta>0.75 and ≤1.25=2; Beta>1.25 and ≤1.75=3; Beta>1.75 and ≤2.25=4; Beta>2.25 and ≤2.75=5; Beta>2.75=6

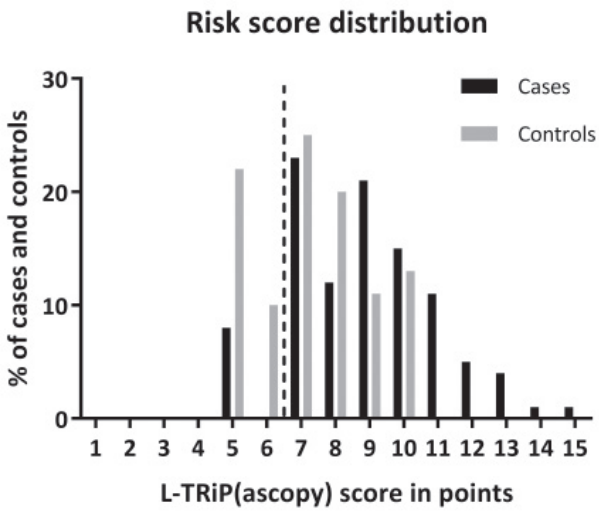

Figure 3. *Risk score distribution among cases and controls for the L-TRiP(ascopy)score (upper figure) and Screening model (lower figure). Dashed black lines represent Cut-off values that correspond to a test sensitivity of approximately 75%.*

Internal and external validation

In the bootstrapped population the Complete and Screening models performed almost as good as in the derivation dataset, whereas the L-TRiP(ascopy) score and Clinical model performed somewhat less well (Table 2). The L-TRiP(ascopy) score resulted in an AUC of 0.67 (95%CI 0.54 – 0.80) while the complete model reached an AUC of 0.78 (95%CI 0.67-0.89).

The population study used for external validation consisted of 784 cases and 523 controls that were included in THE VTE study. 59% of all cases had DVT and 41% had PE with or without DVT. 30 cases and 3 controls had undergone knee arthroscopy within one year before VT. The Complete model resulted in an AUC of 0.75 (95%CI 0.52 – 0.98) and the Screening model yielded an AUC of 0.73 (95%CI 0.49 – 0.96). For our Clinical model and L-TRiP(ascopy) score the AUCs were 0.78 (95%CI 0.48 – 1.00) and 0.77 (95%CI 0.43 – 1.00), respectively. Table 2 gives an overview of the predictive values for all models in both derivation and validation data.

Table 4. *L-TRiP(ascopy) score performance*

Cut point	Sensitivity	Specificity	Sens+Spec	PVV*	NPV*	PVV**	NPV**	Likelihood+	Likelihood-
1	100.0%	0.0%	100.0%	1.50%	100.0%	0.50%	100.0%	1.0	0.0
2	100.0%	0.0%	100.0%	1.50%	100.0%	0.50%	100.0%	1.0	0.0
3	100.0%	0.0%	100.0%	1.50%	100.0%	0.50%	100.0%	1.0	0.0
4	100.0%	0.0%	100.0%	1.50%	100.0%	0.50%	100.0%	1.0	0.0
5	100.0%	0.0%	100.0%	1.50%	100.0%	0.50%	100.0%	1.0	0.0
6	92.3%	21.7%	114.1%	1.77%	99.5%	0.59%	99.8%	1.2	0.2
7	77.8%	40.2%	117.9%	1.94%	99.2%	0.65%	99.7%	1.5	0.2
8	68.8%	64.4%	133.2%	2.86%	99.3%	0.96%	99.8%	1.5	0.4
9	43.2%	84.9%	128.1%	4.17%	99.0%	1.42%	99.7%	1.8	0.4
10	29.0%	99.1%	128.0%	32.15%	98.9%	13.52%	99.6%	3.1	0.6
11	17.9%	100.0%	117.9%	100.00%	98.8%	100.00%	99.6%	29.9	0.6
12	7.1%	100.0%	107.1%	100.00%	98.6%	100.00%	99.5%	21.7	0.7
13	3.6%	100.0%	103.6%	100.00%	98.6%	100.00%	99.5%	∞	0.9
14	1.9%	100.0%	101.9%	100.00%	98.5%	100.00%	99.5%	∞	0.9

**Presuming a prevalence of VT in knee arthroscopy patients of 1.5%*

***Presuming a prevalence of VT in knee arthroscopy patients of 0.5%*

Discussion

Summary of key findings

Patients who undergo knee arthroscopy have an increased risk of developing VT. We developed and validated a prediction model to identify patients at high risk for this complication. Because of the bleeding risk during thromboprophylactic therapy and the low risk of VT, risk stratification is likely to be beneficial, which can be achieved by using the L-TRiP(ascopy) score. Our results indicate that biomarker determination leads to more accurate risk prediction than limiting to clinical variables. However, for clinical practice a clinical model without additional biomarker testing can be preferred until larger validation studies show a strong added value of biomarker testing.

Risk factors for VT in knee arthroscopy patients

A recent cohort study of 12 595 patients found a symptomatic VT incidence of 0.34% (95% CI 0.25 – 0.46) at 4 weeks. Risk factors for VT were: a history of malignancy, a history of VT and the presence of two or more risk factors according to Delis (age>65, BMI>30, smoking, use of oral contraceptives or hormonal replacement therapy, chronic venous insufficiency, history of VT).[2] A similar incidence of 0.46% (95% CI 0.43 - 0.49) was found by Bohensky and colleagues, in a cohort study with 180 717 arthroscopies.[20] In this study only chronic kidney disease was found to be a clear risk factor for the development of VT while patients with cancer, peripheral vascular disease, chronic heart failure, cerebrovascular event, myocardial infarction, chronic lung disease, hemiplegia or diabetes were not at increased risk after arthroscopy. A study from New York reported on predictors of pulmonary embolism following a knee arthroscopy among 418 323 operations. The 30-day incidence was 2.8 per 10 000 knee arthroscopies and risk factors for the development of VTE were age>30, female sex, history of cancer and an operating time over 90 minutes. Type of surgery or presence of comorbidity was not associated with VT.[21] Another observational study with 4 833 patients undergoing arthroscopic surgery showed that only older age and hospitalization in the preceding 3 months were predictors of VT.[3]

All these studies had an observational design, and information bias cannot be ruled out: Data on comorbidities were collected using large hospital or nationwide databases. Data collection or reporting on putative risk factors may have been more rigorous for patients with VT than for those without, which could be an explanation for the contradicting results on different risk factors as shown by several of these studies. Also, logistic

regression analyses in these studies were often underpowered because of the low incidence rate and scarce distribution of risk factors. In our study cases and controls were asked to complete questionnaires about their health one year prior to the VT date or a random control date, respectively (this active approach reduced the risk of bias). The number of cases in our study used for the regression analysis (n=4 943) is much more than the total number of events in previous studies. Therefore, the predictive values of various risk factors, derived from all patients, are more accurate in our study. Furthermore, prediction of high-risk patients in this population with a low incidence of VT is more valuable than identifying individual risk factors. Our goal was therefore not to estimate associations of single risk factors, but to combine all information for optimal individual risk stratification.

Specific aspects of the patient population that undergoes knee arthroscopy may also have contributed to the conflicting results that have been reported. In the study from New York, 92.3% of all patients had a Charlson/Deyo comorbidity score of 0, meaning that they had no history of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, liver disease, diabetes mellitus, (para)plegia, renal disease or AIDS.[21] Similar patient characteristics were reported by Jameson, where 90% had a Charlson/Deyo score of 0 and the mean age was 45.9 years.[22] These studies illustrate that patients undergoing knee arthroscopy are in general young and healthy with only very few comorbidities. Consequently, while comorbidity is associated with VT risk in other situations, there is limited contribution of environmental risk factors to risk stratification in the arthroscopic population. A similar problem exists when using other prediction scores for VT, for instance the Caprini score[23]. According to this score, patients who undergo arthroscopic surgery score 2 points, indicating a moderate risk for VT. Consequently, all patients who undergo arthroscopy receive thromboprophylaxis and a further discrimination between low- and high-risk patients within a surgical subgroup (such as knee arthroscopy), cannot be made.

Given the young and healthy population with few environmental risk factors, we investigated the additional predictive value of biomarkers (that are easy to determine in a clinical setting). To our knowledge, this has not been done in knee arthroscopy patients for the development of VT to date. We found that addition of FVIII concentration (FVIII;C), vWF activity, Factor V Leiden mutation (FV Leiden) and monocyte percentage

to our model increased the predictive value. However, to improve clinical usefulness we attempted to minimalize the number of biomarkers. Out of the biomarkers that were associated we chose to incorporate FVIII in the Screening model for practical reasons. The Screening model performed slightly better than the L-TRiP(ascopy) score, (AUC difference in derivation study 0.03 points, and 0.07 point in internal validation). Our external validation study was not powered sufficiently to clearly show a beneficial effect of FVIII, and all models performed roughly similarly (AUC range 0.75-0.78). Therefore, we finally opted to convert the Clinical model in the L-TRiP(ascopy) score, rather than the Screening model as the predictive value of adding a biomarker did not outweigh the hassle of measuring factor VIII (in terms of costs, and logistics in routine clinical care). However, it should be kept in mind that due to less discriminatory power, there will be overtreatment of controls (Table 4).

Limitations of the study

Our study lacked information on thromboprophylaxis therapy after knee arthroscopy for all individuals. However, in a survey study in the Netherlands which was performed during the same period as the inclusion period of our case-control study, 71% of all orthopedic surgeons stated that they used a low-molecular-weight-heparin (LMWH) for prophylactic therapy in patients undergoing a knee arthroscopy in most cases. 91% of these surgeons only used a single-dose of LMWH.[24] This could have affected the actual risk in our patient population. Nevertheless, the therapeutic value of a single dose of LMWH is not known and probably limited. In addition, as we recently showed that thromboprophylaxis is not effective for VT prevention following knee arthroscopy[12], the effect of prophylaxis on VT development (and thus on model development) is negligible. Furthermore, the L-TRiP(ascopy) model was developed by identifying candidate predictors using all cases and controls from the MEGA study. Beta-coefficients and risk points in the final risk score were based on many patients, thereby preventing over-fitting. An additional internal validation showed similar performance statistics, indicating the robustness of model performance. Also, our validation cohort did not include sufficient numbers of patients (especially control subjects) with knee arthroscopy to obtain precise results. Validation results were therefore not very precise, however, all models performed promisingly and were in line with the derivation results. To account for this problem, an internal validation was performed to confirm our findings, which showed similar results. However, a larger validation study (and perhaps a cost-

effectiveness study) is still needed to confirm our results and to determine if biomarkers are needed to improve risk prediction following knee arthroscopy.

Clinical implications

To date, there is no consensus on thromboprophylactic therapy for patients who underwent knee arthroscopy. However, we recently published a large randomized controlled trial (POT-KAST trial) that showed a lack of effectiveness for thromboprophylaxis for 8 days after knee arthroscopy (1451 patients).[12] In this trial, still 0.6% of patients developed a thrombotic event and these patients had several additional risk factors for VT. Our L-TRiP(ascopy) score can be a helpful tool to guide doctors in their decision on anticoagulant treatment for those patients at high risk for VT. Since we showed that a prophylactic dose of anticoagulant therapy does not prevent VT, other treatment regimens (such as a longer therapy duration or higher dosage) might be effective in those patients with an extremely high risk, but should also be restricted to this group, considering the high bleeding risk, which is currently about 0.5% major and clinically relevant non-major bleeding.[12]. Increasing the duration and dosage of thromboprophylaxis will likely lead to a further increased bleeding risk. Since bleeding risk is already nearing VTE risk, it is crucial to identify only those patients with the highest VTE risk in order to optimize patient care. To accomplish this, a score with a high sensitivity and high specificity is desirable, in which case we would only treat those patients at high risk without giving treatment to patients who will not develop VT. The L-TRiP(ascopy) score can have a high sensitivity, for example, a cut off score of 7 or higher results in a sensitivity of 77.8%. However, the corresponding specificity is only 40.2%, which implies that many controls would also receive treatment, leading to unnecessary bleeding events and costs. Determining the right cut-off for risk discrimination is therefore not straightforward, especially because of the uncertainty in the specificity of our score, which is only based on 26 controls. Ideally, the absolute risks corresponding with our L-TRiP(ascopy) score should be calculated in a large prospective study so that the optimal cut-off can be determined.

Conclusion

Given the lack of effectiveness of thromboprophylactic therapy in all patients who undergo knee arthroscopy, an alternative strategy might be to identify those individuals at high risk of developing VT and provide stronger treatment for this group. We developed the L-TRiP(ascopy) score that may be suitable for this purpose. However,

a larger validation study is needed to confirm our results and to determine a definite cut-off for high risk patients.

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Supplement material

Detailed information on laboratory analyses.

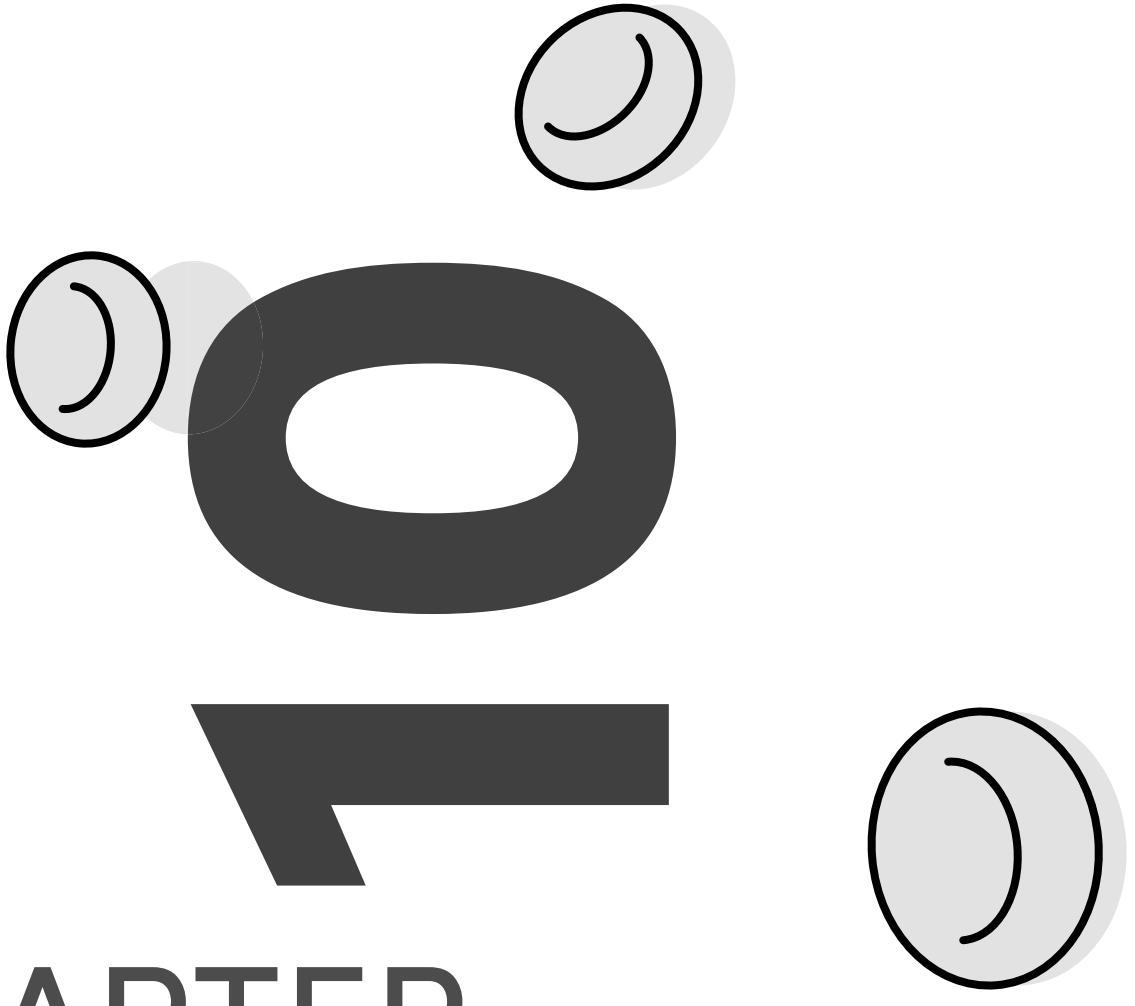
Coagulation markers such as pro-thrombin activity (factor II [FII]), FVII activity, FVIII activity, anti-thrombin (AT) activity, protein C (PC) activity and protein S (PS) antigen level were measured with a mechanical clot detection method on a STA-R coagulation analyzer following the instructions of the manufacturer (Diagnostica Stago, Asnieres, France). Levels of FIX antigen were determined by enzyme-linked immunosorbent assay (ELISA). Fibrinogen activity was measured on the STA-R analyzer according to methods of Clauss. In the presence of excess thrombin, the coagulation time of a diluted plasma sample was measured. 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). Immunologic markers such as hematocrit, white blood cell count (WBCC), percentage/number lymphocytes, percentages/number monocytes, percentage/number granulocytes, red blood cell count (RBCC), hemoglobin level, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), red cell distribution with (RDW), anti-thrombin activity, total homocysteine, total cysteine, methionine and FX antigen level were measured using the Beckman coulter analyzer. FV Leiden (F5, rs6025) and the pro-thrombin G20210A (F2, rs1799963) mutation were measured simultaneously by a multiplex polymerase chain reaction using the TaqMan assay. ABO-blood group was also analyzed using the TaqMan assay

Missing data and multiple imputation

Multiple imputations were used to complete missing predictor values, of which the table below gives an overview. Data on environmental risk factors were collected by means of a questionnaire, and missing data on the questionnaire resulted in this missing data at random. Blood collection was terminated for logistic reasons on 31 May 2002. For participants included after this date no blood was sampled which resulted in missing data completely at random. For patients included after 31 May 2002, buccal swabs were collected for deoxyribonucleic acid analyses. Patients who did not return their buccal swab created these missing data.

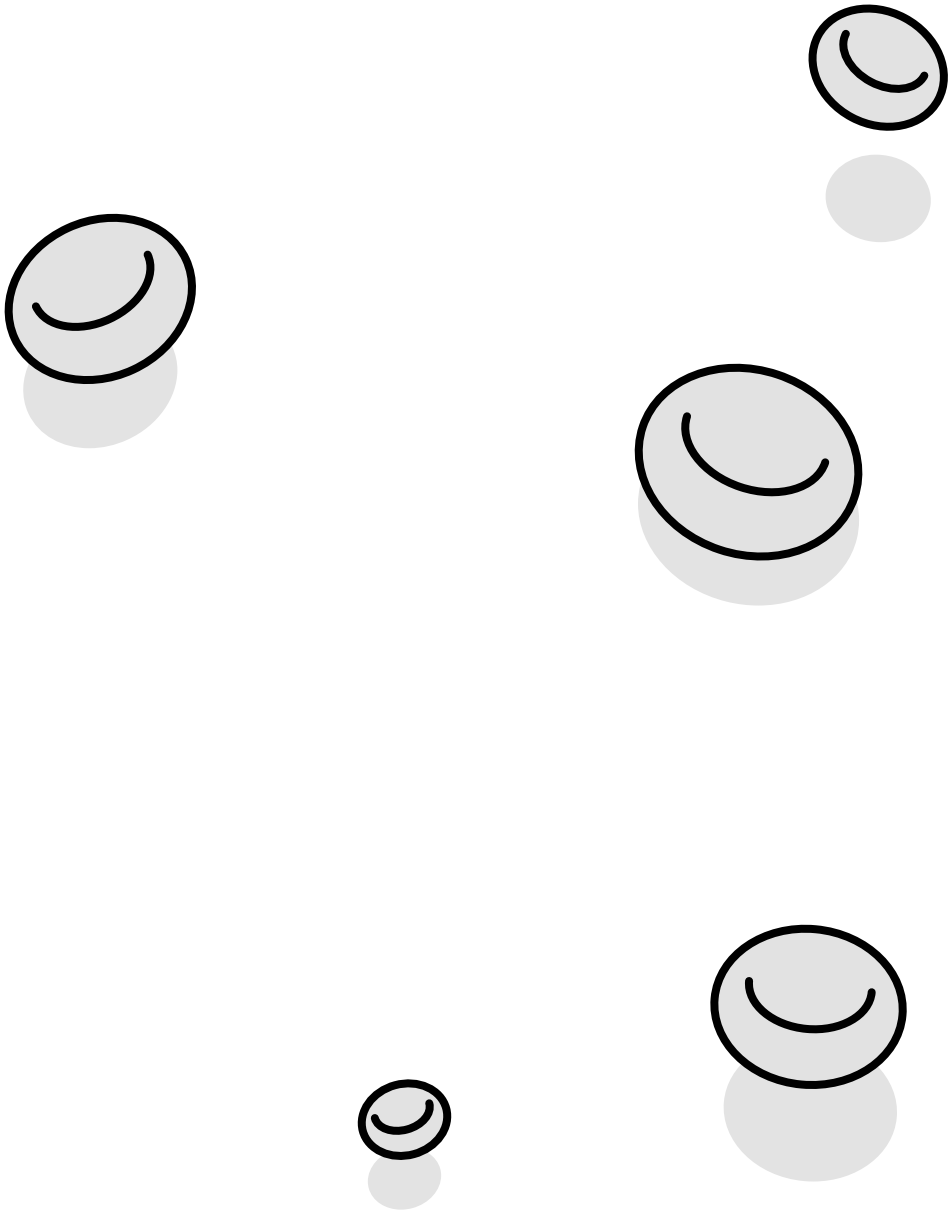
Table. *Percentage of missing values of predictor variables*

Predictor variables	Percentage missing %
Environmental predictor variables	
Varicose veins	17.1
Congestive heart failure	10.9
Family history of venous thrombosis	29.3
Bedridden for the past 3 months	1.3
Current use of oral contraceptives	0.6
Immunologic and coagulation predictor variables	
Factor VIII activity	52.8
Von Willebrand factor	52.8
Percentage monocytes	53.6
Genetic predictor variables	
Factor V Leiden mutation	18.8



CHAPTER

Summary and general discussion



Orthopedic surgery is well recognized as a risk factor for venous thromboembolism (VTE) and the use of thrombosis prophylaxis is recommended for most orthopedic procedures.[1,2] However, for knee arthroscopy and lower leg cast immobilization, the magnitude of this risk has previously not been studied thoroughly, limiting clear recommendations for thrombosis prophylaxis.[1-3]

In this thesis the magnitude of the risk of symptomatic VTE, the combined effects of genetic and acquired risk factors, the current prophylactic strategies in the Netherlands, the effect of thrombosis prophylaxis on risk reduction of symptomatic VTE (in contrast to asymptomatic VTE), the predictive value of environmental, genetic risk factors and biomarkers for the development of VTE and the prediction of events in patients with lower leg cast immobilization and after knee arthroscopy have been studied.

Overview of main findings

Thrombosis risk in lower leg cast immobilization

The risk of VTE associated with cast immobilization of the lower leg is described in chapter 2. A 56-fold increased VTE risk compared to the general population was found in the first 3 months of lower leg cast immobilization. In these first 3 months 90% of the cases occurred. This corresponds to an estimated absolute risk of VTE of 1% in 3 months (based on an incidence of 0.75 per 1000 person-years in the general population).[4] In addition, a higher risk of VTE was found in patients treated with cast immobilization for a trauma to the lower leg compared to non–traumatic indications. A further increased risk was found for patients with well-known genetic risk factors (factor V Leiden mutation and prothrombin G20210A mutation) and additional acquired risk factors (i.e. obesity and oral contraceptive use). The presence of a combination of these risk factors led to an even further increased risk.

Thrombosis risk after knee arthroscopy

In Chapter 3 the risk of VTE after knee arthroscopy is given. In the 3-months after the procedure a 16-fold increased risk compared to the general population was found. Once again, this risk was highest in the first weeks after knee arthroscopy, and no additional increased risk was found after three months. Different types of arthroscopic procedures showed different VTE risks, with a higher risk for anterior cruciate ligament reconstruction compared to less invasive procedures such as meniscal surgeries,

diagnostic arthroscopies or chondroplasties (i.e., a 17-fold increased risk vs a 5-fold increased risk in one year after the procedure). The combination of knee arthroscopy with the presence of well-known genetic and other acquired risk factors in patients (e.g. FV Leiden, Prothrombin G20210A mutation, non-O blood group, or oral contraceptives) resulted in an additionally increased risk. These distinct differences in the risk of VTE between individuals after knee arthroscopy and during lower leg cast immobilization was the basis for the identification of high-risk patients using prediction models in chapter 8 and 9.

Current treatment strategies

Because of the lack of solid evidence, national and international guidelines recommend against thromboprophylaxis after knee arthroscopy and during lower leg cast immobilization. [1-3] However, as shown in chapter 4, the vast majority of patients with lower leg cast immobilization in the Netherlands receives thrombosis prophylaxis with Low Molecular Weight Heparin (LMWH) (79% of trauma surgery and 63% of orthopedic surgery departments). In general, LMWH is given for the duration of immobilization (96% and 89% of trauma and orthopedic surgery departments respectively). With respect to knee arthroscopy, the decision to give prophylaxis depends on the type of arthroscopic knee surgery. Thrombosis prophylaxis is given to around one third of patients with a diagnostic arthroscopy, loose body removal surgery or partial meniscectomy. In contrast, if a more invasive procedure, such as an anterior cruciate ligament (ACL) reconstruction, is performed over 75% of patients are given prophylaxis. The duration of prophylactic treatment is also dependent on the type of arthroscopic knee surgery and varied between 1 day (most frequent) to 1 week (e.g. for diagnostic procedures, loose body removal and partial meniscectomy) and (most frequent) between 3 to 6 weeks after ACL reconstruction. The rationale for thromboprophylactic therapy was the assumption that the risk reduction for thrombosis outweighed the bleeding risk, the experience of clinicians that thromboprophylaxis is effective and that clinicians act in accordance with a department or hospital protocol. This widespread use of thrombosis prophylaxis in these patients despite clear-cut evidence for a beneficial effect shows that good quality research was needed to improve the quality of care for patients.

Effect of thrombosis prophylaxis during lower leg cast immobilization

The results of a large pragmatic randomized clinical trial studying the effect of low-molecular weight heparin (LMWH) on the prevention of symptomatic venous

thromboembolism compared to no treatment during cast immobilization is given in chapter 5. In total over 1500 patients were included, of which half were allocated to prophylactic treatment with LMWH and half to no treatment. The cumulative incidence of symptomatic VTE in three months for patients in the LMWH therapy group was 1.4% (95%CI: 0.7 – 2.5) vs 1.8% (95%CI: 1.0 – 3.0) in the no treatment group (RR 0.8 (95%CI: 0.3 – 1.7) and RD -0.4 (95%CI -1.8 – 1.0)). This corresponds to a high number needed to treat of 250 patients to prevent one symptomatic event. Therefore, we were unable to show a beneficial effect for prophylactic treatment with anticoagulants during the period of lower leg cast immobilization. With no major bleedings and only 1 clinically relevant non major bleeding in this study, treatment with prophylactic dosage of LMWH was relatively safe, however not beneficial. In addition, treatment with anticoagulants comes with additional costs and, in case of LMWH, with the burden of daily injections. Clinicians should therefore not routinely give thrombosis prophylaxis to patients treated with lower leg cast immobilization.

Effect of thrombosis prophylaxis after knee arthroscopy

In chapter 6 the results of the POT – KAST trial (prevention of thrombosis after knee arthroscopy) are given. In this large randomized trial, over 1500 patients who had knee arthroscopy were included of which half were allocated to thromboprophylaxis with LMWH for 8 days and half were allocated to no treatment. The cumulative VTE risk in three months in both groups was low: 0.7% (95%CI: 0.3 – 1.7) for treatment with LWMH and 0.4% (95%CI: 0.3 – 1.7) for no treatment. Therefore, no beneficial effect of prophylactic LMWH was found (RR 1.6 (95%CI: 0.4 – 6.8)). Treatment with a prophylactic dose of LMWH was relatively safe. In both groups 1 major bleeding event occurred and 1 clinically relevant non-major bleed occurred in the LMWH group compared to 3 events in the no-treatment group. Although treatment is relatively safe, because of a lack of beneficial effect we recommend that routine thrombosis prophylaxis should not be given after knee arthroscopy. Both in the trial in patients with lower leg cast immobilization and in the trial in patients who had knee arthroscopy, patients still developed VTE despite prophylactic treatment. A prophylactic dose of LMWH might not be sufficient for these patients. Providing a higher dose of LMWH to all patients is, however, expected not to be beneficial, as this would increase the bleeding risk. Therefore, instead of providing high dose prophylactic treatment to all patients, the aim of our future research will be on risk prediction in order to be able to identify high risk

groups and thus provide (higher or prolonged dose) thrombosis prophylaxis selectively to patients with an increased VTE risk.

Effect of thrombosis prophylaxis after anterior cruciate ligament (ACL) reconstruction

Because ACL reconstruction is estimated to have a higher VTE risk than regular knee arthroscopy (see chapter 3), thrombosis prophylaxis in these patients has been studied separately. In chapter 7, the results of an instrumental variable analysis comparing two orthopedic surgery centers with different VTE prophylaxis policies but otherwise identical treatment protocols and similar patient populations (an observational study design of which the results can be interpreted as if it were a randomized clinical trial) is given. The additional effect of pharmacological thrombosis prophylaxis with LMWH to prophylaxis with a compression stocking on the incidence of VTE after an ACL reconstruction was studied. We found no difference in the occurrence of symptomatic VTE in these patients (RR 1.9 (95%CI; 0.2 – 11.8)). Furthermore, the incidence of symptomatic VTE in both groups was low (0.23% (95%CI; 0.01 – 1.41) vs 0.43% (95%CI; 0.12 – 1.14)). Therefore, we advise not to give thrombosis prophylaxis with LMWH, with its associated burden and risks, routinely to this generally young and healthy group of patients, in whom the VTE risk is very low. Once again, anticoagulant therapy might be beneficial in certain high-risk patients. Identifying high risk groups and selective treatment of these patients could reduce thrombosis morbidity and the risk of treatment complications.

Risk prediction and prevention of future events

Patients treated with lower leg cast immobilization or arthroscopy of the knee have an increased risk of venous thrombosis (chapter 2 and 3). However, as shown in chapter 5 and 6, a prophylactic dose of LMWH provided to all these patients did not decrease the risk of VTE. Selective treatment and identification of high-risk patients could therefore be beneficial. Consequently, the predictive value of genetic and environmental risk factors, coagulation factors and other biomarkers for the development of VTE during cast immobilization of the lower extremity (chapter 8) and after arthroscopy of the knee was studied (chapter 9). In addition, prediction models for the development of VTE in these patients were developed and validated (chapter 8 and 9).

Three risk prediction models were made for the development of VTE in patients with lower leg cast immobilization (chapter 8). A full model containing 32 predictors (including three genetic and six biomarkers), a restricted model (11 predictors, including two genetic and one biomarker) and a clinical model containing only environmental risk factors (14 predictors) which are easy to determine. All had good predictive value with an area under the curve (AUC) of the receiver operating characteristic (ROC) of 0.85 (95%CI: 0.77 – 0.92), 0.84 (95%CI: 0.77 – 0.92) and 0.77 (95%CI: 0.66 – 0.87) respectively. Validation of these prediction models in two other studies showed comparably good results. The clinical model was converted into a risk score based on points assigned to the regression coefficients of the predictor variables. With an AUC of 0.76 (95%CI: 0.66 – 0.86) results of the risk score were similar to the clinical model, external validation of the score showed comparable results.

In analogy to the development of prediction models for patients with lower leg cast immobilization, prediction models for the development of VTE after knee arthroscopy were developed (chapter 9). In addition to a full model and a restricted model (containing genetic risk factors and biomarkers), a clinical model with a corresponding risk score for daily clinical practise was developed. The clinical model included 8 environmental risk factors and resulted in an AUC of 0.72 (95%CI: 0.60 – 0.83). The corresponding risk score resulted in an AUC of 0.73 (95%CI: 0.63 – 0.84). External validation showed similar results.

Because the risk scores include only easy to determine environmental risk factors, these risk scores can provide guidance for the prescription of thrombosis prophylaxis in patients with lower leg cast immobilization and after arthroscopy of the knee in a clinical setting.

Conclusions, implications and future directives

Despite having an increased risk of venous thrombosis (chapter 2 and 3), the use of routine low dose LMWH as thrombosis prophylaxis did not decrease the risk of VTE in patients with lower leg cast immobilization nor in patients after arthroscopy of the knee (chapter 5 and 6). Because of this lack of a beneficial effect, we recommend no routine thrombosis prophylaxis with anticoagulants to these patients (chapter 5 and 6). Different treatment strategies, such as a higher dose of anticoagulant treatment or even longer duration of treatment might be beneficial in these patients. However, such

a policy will most likely also increase the risk of bleeding due to anticoagulant treatment. We have shown that the risk of VTE varies among patients based on the presence of additional acquired and genetic risk factors (chapter 2 and 3). Furthermore, these risk factors can be used in predicting the risk of VTE in these patients by means of prediction models (chapter 8 and 9). Hence, identification of high-risk patient can help to optimize prophylactic treatment: providing a higher dose or longer duration of anticoagulant treatment to patients with an additionally increased risk, whilst patients with a low risk will not be needlessly exposed to the burden and risk of anticoagulants. Our prediction models (Chapter 8 and 9) can give guidance in selecting these high-risk patients who can benefit from additional prophylactic therapy. The effect of selectively providing a higher dose or longer duration of treatment based on these prediction models, however, needs to be further investigated, ideally in a randomized trial comparing this strategy to no prophylactic therapy.

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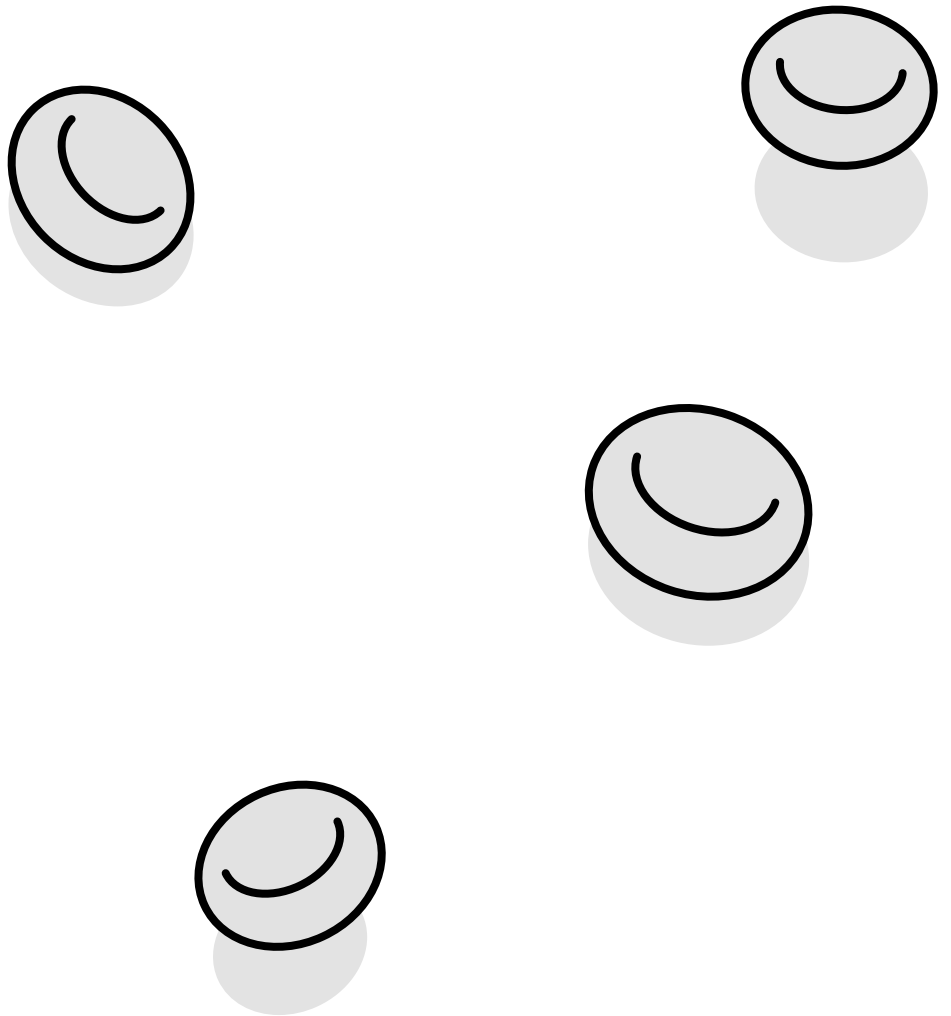
CHAPTER

List of publications
Nederlandse samenvatting
Dankwoord
Curriculum vitae



List of publications

Publications related to this thesis

Venous Thrombosis Risk after Arthroscopy of the Knee: Derivation and Validation of the L-TRIP(ascopy) Score.

B. Nemeth, R.A. van Adrichem, A. van Hylckama Vlieg A, T. Baglin, F.R. Rosendaal, R.G.H.H. Nelissen, S. le Cessie, S.C. Cannegieter.

Thromb Haemost 2018; 118:1823-31

Thromboprophylaxis after Knee Arthroscopy and Lower-leg Casting.

R.A. van Adrichem, B. Nemeth*, A. Algra, S. le Cessie, F.R. Rosendaal, I.B. Schipper, R.G.H.H. Nelissen, S.C. Cannegieter for the POT-KAST study group * Authors contributed equally

New Engl J Med 2017; 376:515-25

Venous Thrombosis Risk after Cast Immobilization of the Lower Extremity: Derivation and Validation of a Clinical Prediction Score, L-TRiP(cast), in Three Population-Based Case-Control Studies.

B. Nemeth, R.A. van Adrichem, A. van Hylckama Vlieg, P. Bucciarelli, I Martinelli, T. Baglin, F.R. Rosendaal, S. le Cessie, S.C. Cannegieter.

PLoS Med 2015;12:e1001899

Thromboprophylaxis for lower leg cast immobilization and knee arthroscopy: a survey study.

R.A. van Adrichem, J.P. van Oosten, S.C. Cannegieter, I.B.Schipper, R.G.H.H. Nelissen.

Neth Jour of Med 2015;72:23-9

Risk of venous thrombosis after arthroscopy of the knee: results from a large population-based case-control study.

R.A. van Adrichem, R.G.H.H. Nelissen, I.B. Schipper, F.R. Rosendaal, S.C. Cannegieter

J Thromb Haemost 2015;13:1441-8

Below-knee cast immobilization and risk of venous thrombosis: results from a large population-based case-control study.

R.A. van Adrichem, J. Debeij, R.G.H.H. Nelissen, I.B. Schipper, F.R. Rosendaal, S.C. Cannegieter

J Thromb Haemost 2014;12:1461-9

De Pot-(K)Cast studie: tromboseprofylaxe na artroscopie van de knie en bij onderbeengipsbehandeling: wegen de risico's op tegen de voordelen?

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Invited Lectures

Pot-Cast trial – Prevention of Thrombosis during Cast Immobilisation

Traumadagen November 2017, Amsterdam, the Netherlands

Chirurgendagen may 2017, Veldhoven, the Netherlands

Oral presentations

Pot-Cast trial – Prevention of Thrombosis during Cast Immobilisation

EFFORT, May 2017, Vienna, Austria

Preventie van veneuze trombose na een voorste kruisband reconstructie: laagmoleculair-gewicht heparine en thromboembolic deterrent stocking

NOV conference, February 2015, Maastricht, the Netherlands

Arthroscopy of the knee and the risk of venous thrombosis – Results from the MEGA study

ISTH, July 2013, Amsterdam, the Netherlands

NvTH Symposium April 2013, Koudekerke, the Netherlands

Cast immobilization of the lower leg and the risk of symptomatic venous thrombosis – Results from the MEGA study

ISTH, July 2013, Amsterdam, the Netherlands

NvTH Symposium April 2012, Koudekerke, the Netherlands

Traumadagen November 2011, Amsterdam, the Netherlands

Poster presentations

Prevention of venous thrombosis after an anterior cruciate ligament reconstruction: compression stockings alone versus its combination with low molecular weight heparin

ISTH, July 2015, Amsterdam, the Netherlands

Prediction of risk of venous thrombosis after cast immobilization of the lower extremity

ISTH, July 2013, Amsterdam, the Netherlands

Awards and honours

Nominee VGZ zinnige zorg award, *VGZ 2018, the Netherlands*

LUMC Best Article Prize (clinical), *LUMC 2017, the Netherlands*

Nominated for Biomet Award for best scientific oral presentation, *NOV 2015, the Netherlands*

Young Investigator Award, *ISTH 2013, the Netherlands*

Award of Excellence, *NvTH 2012, the Netherlands*

Nederlandse Samenvatting (Summary in Dutch)

Achtergrond

Veneuze trombose is de verzamelnaam voor diep veneuze trombose en longembolie, waarbij diep veneuze trombose ongeveer twee keer zo vaak voorkomt als een longembolie. Veneuze trombose is, na een myocardinfarct en een herseninfarct of bloeding, de derde meest voorkomende cardiovasculaire ziekte. Het overlijdensrisico van een veneuze trombose is hoog, daarnaast kan het lijden tot chronische ziekte, zoals post-trombotisch syndroom na een diep veneuze trombose, of pulmonale hypertensie na een longembolie.

Veneuze trombose kent veel risicofactoren, zowel genetische als verworven. Een belangrijke risicofactor is orthopaedische chirurgie. Om deze reden wordt tromboseprofylaxe voor de meeste orthopaedische behandelingen geadviseerd. Het risico op veneuze trombose varieert echter per orthopaedische behandeling en is niet voor alle orthopaedische ingrepen even goed bekend. Dit is bijvoorbeeld het geval voor patiënten die worden behandeld met onderbeengips en na arthroscopie van de knie (terwijl arthroscopie van de knie, met meer dan vier miljoen ingrepen per jaar, de meest voorkomende orthopaedische behandeling wereldwijd is). Voor deze patiëntengroepen is het dan ook onduidelijk of tromboseprofylaxe geïndiceerd is.

Het doel van dit proefschrift was dan ook om de hoogte van het risico op veneuze trombose te bestuderen tijdens behandeling met onderbeengips en na arthroscopie van de knie, welke factoren van invloed zijn op dit risico en het effect van tromboseprofylaxe met antistollingsmedicatie.

Overzicht van de belangrijkste resultaten van dit proefschrift

Tromboserisico in patiënten met onderbeengips en na een arthroscopie van de knie

In Hoofdstuk 2 en 3 wordt het risico op veneuze trombose tijdens gipsimmobilisatie en na arthroscopie van de knie beschreven. Daarnaast wordt de invloed van bekende genetische en verworven risicofactoren op het trombose risico in deze patiënten beschreven.

In patiënten met gipsimmobilisatie was er een 56-maal verhoogd risico op veneuze trombose in 3 maanden na start gipsimmobilisatie in vergelijking met de algemene bevolking. Voor arthroscopie van de knie was dit een 16-maal verhoogd risico in 3 maanden. Dit komt overeen met een geschat absoluut risico op veneuze trombose van 1% in 3 maanden bij patiënten met onderbeengips en 0.3% in de 3 maanden na arthroscopie van de knie. In beide groepen is het risico het hoogst in de eerste weken na behandeling en is er geen verhoogd risico meer na 3 maanden. Voor meer invasieve arthroscopische behandelingen, zoals een voorste kruisbandreconstructie, was het risico hoger dan na minder invasieve arthroscopische ingrepen zoals een meniscectomie of een diagnostisch procedure. Zowel voor patiënten met onderbeengips als na een arthroscopie van de knie werd een verder verhoogd risico gevonden bij patiënten met een bekende genetische risico factor voor veneuze trombose (Factor V Leiden, Prothrombine 20210A mutatie, non-O bloedgroep) of voor verworven risicofactoren (obesitas en gebruik van orale anticonceptie ('de pil')). Het gevonden verdere hogere risico op veneuze trombose in patiënten met aanvullende risicofactoren diende als basis voor de identificatie van hoog-risicopatiënten met behulp van predictiemodellen. Dit wordt in hoofdstuk 8 en 9 verder beschreven.

Tromboseprofylaxe in Nederland

Nationale en internationale richtlijnen geven het advies geen tromboseprofylaxe te gebruiken tijdens onderbeengips of na arthroscopie van de knie omdat eerder onderzoek hierin niet eenduidig is. Om inzicht te krijgen in het gebruik van tromboseprofylaxe bij deze patiënten in Nederlandse ziekenhuizen werd in 2013 een enquêtestudie onder orthopaedisch chirurgen en traumachirurgen verricht. De resultaten hiervan worden beschreven in Hoofdstuk 4. Hieruit bleek dat het overgrote deel van de patiënten met onderbeengips tromboseprofylaxe met antistollingsmedicatie (te weten laagmoleculairgewichtheparine) voorgeschreven kreeg. Dit was het geval in 79% van de traumachirurgie en 63% van de orthopaedische chirurgie afdelingen. Voor arthroscopie van de knie hing het gebruik van tromboseprofylaxe met antistollingsmedicatie af van de indicatie van de ingreep. Patiënten met invasievere behandelingen, zoals een voorste kruisbandreconstructie, kregen op 75% van de orthopaedisch chirurgische afdelingen antistollingsmedicatie terwijl voor minder invasieve ingrepen (te weten een diagnostische scopie, verwijderen van losse fragmenten in het gewricht of een meniscectomie) dit in ongeveer 33% het geval was. Ook werden de patiënten met minder invasieve ingrepen aanzienlijk korter behandeld (gemiddeld 1 dag tot 1 week)

terwijl na een voorste kruisbandreconstructie het merendeel van de patiënten 3 tot 6 weken antistollingsmedicatie voorgeschreven kregen. De variatie in behandeling gaf aan dat er behoefte was aan onderzoek van goede kwaliteit om tot uniforme behandelstrategieën te komen.

Effect van tromboseprofylaxe bij onderbeengips en na arthroscopie van de knie

In hoofdstuk 5 en 6 worden de resultaten van twee pragmatische multicenter gerandomiseerde klinische trials beschreven naar het effect van tromboseprofylaxe met antistollingsmedicatie (laagmoleculairgewichtheparine) bij patiënten met onderbeengips (de Pot-Cast studie) en bij patiënten die een artroscopie van de knie ondergingen (de Pot-Kast studie). Aan beide studies hebben meer dan 1500 patiënten deelgenomen, waarvan de helft van de patiënten met onderbeengips en de helft van de patiënten na een arthroscopie van de knie op basis van loting tromboseprofylaxe met antistollingsmedicatie voorgeschreven kregen. Op deze manier kan een reële schatting van het effect van antistollingsmedicatie op het voorkomen van een veneuze trombose bij deze patiëntengroepen gegeven worden. Bij patiënten met onderbeengips was het verschil in veneuze trombose tussen de behandelde groep en onbehandelde groep klein (1.8% in 3 maanden in de onbehandelde groep en 1.4% in 3 maanden in de behandelde groep) en kon er geen relevant voordeel van behandeling met antistollingsmedicatie aangetoond worden. Ook na een arthroscopie van de knie kon geen relevant voordeel van behandeling met antistollingsmedicatie aangetoond worden. In beide groepen was het optreden van veneuze trombose laag, 0.4% in de onbehandelde groep en 0.7% in de behandelde groep (beiden in 3 maanden). Bloedingen, de keerzijde van antistollingsmedicatie, kwamen slechts enkele keren voor in beide studies. Ondanks dat het gebruik van antistollingsmedicatie relatief veilig lijkt, is door het gebrek aan relevante risicovermindering op het optreden van veneuze trombose het advies geen tromboseprofylaxe met antistollingsmedicatie te gebruiken in patiënten met onderbeengips en na arthroscopie van de knie. In beide patiëntengroepen ontwikkelden patiënten nog steeds een veneuze trombose ondanks het gebruik van antistollingsmedicatie. Het gebruik van een hogere dosis antistollingsmedicatie zou mogelijk het optreden van een veneuze trombose kunnen reduceren, maar gaat waarschijnlijk gepaard met een hoger bloedingsrisico en is daardoor onaantrekkelijk. In plaats van alle patiënten behandelen met een hogere dosis antistollingsmedicatie lijkt het zinvoller om hoog-risicopatiënten op het ontwikkelen van veneuze trombose,

vanwege de aanwezigheid van aanvullende risicofactoren, te identificeren en hen selectief aanvullend te behandelen.

Effect van tromboseprofylaxe na een voorste kruisbandreconstructie

In hoofdstuk 3 is beschreven dat een voorste kruisbandreconstructie een hoger risico op veneuze trombose kent dan minder invasieve vormen van arthroscopie van de knie. Om die reden is deze groep patiënten apart bestudeerd. In hoofdstuk 7 wordt het resultaat van een studie, uitgevoerd in twee orthopaedische behandelcentra, beschreven. Hoewel beide behandelcentra nog geen 10 km uit elkaar liggen, worden patiënten in het ene centrum behandeld met een steunkous als tromboseprofylaxe na een voorste kruisbandreconstructie, terwijl zij in het andere centrum een steunkous en antistollingsmedicatie (laagmoleculairgewichtheparine) krijgen. Omdat operatieprocedures en nabehandelingsprotocollen verder vergelijkbaar zijn bood dit een ideale situatie om deze centra met elkaar te vergelijken en het effect van aanvullende behandeling met antistollingsmedicatie te bestuderen. Wederom was het risico op het optreden van een veneuze trombose laag en vergelijkbaar in beide groepen (0.23% in de groep met een steunkous en 0.43% in de groep met een steunkous en antistollingsmedicatie, beiden in 3 maanden na reconstructie). Wederom is derhalve het advies geen antistollingsmedicatie te gebruiken in deze patiënten. Patiënten die een voorste kruisbandreconstructie ondergaan zijn over het algemeen jonge en gezonde patiënten. Selectie van patiënten met aanvullende risicofactoren voor een veneuze trombose en selectieve behandeling hiervan zou mogelijk het tromboserisico verder kunnen verminderen.

Risicopredictie voor veneuze trombose bij gipsimmobilisatie en na arthroscopie van de knie

Zoals beschreven in hoofdstuk 2 en 3 is er een verhoogd risico op veneuze trombose na onderbeengips en na arthroscopie van de knie (inclusief voorste kruisbandreconstructie). Echter zoals beschreven in hoofdstuk 5, 6 en 7 is er geen bewezen voordeel van het gebruik van antistollingsmedicatie bij al deze patiënten ten aanzien van het voorkomen van veneuze trombose. Identificatie van hoog-risicopatiënten en selectieve behandeling van deze patiënten (eventueel met een hogere dosis antistollingsmedicatie) zou het optreden van veneuze trombose na deze ingrepen mogelijk verder kunnen verminderen. Om die reden zijn predictiemodellen ontwikkeld en gevalideerd voor het voorspellen van veneuze trombose na arthroscopie van de knie en bij patiënten met onderbeengips

(hoofdstuk 8 en 9). Voor beide patiëntengroepen is zowel een model met verworven risicofactoren, bloedwaarden en genetische factoren (voor maximale accuratesse), als een model met alleen verworven risicofactoren ontwikkeld. Beide modellen lieten een goede voorspellende waarde zien. Het model met alleen verworven risicofactoren kan eenvoudiger in de klinische praktijk gebruikt worden. Derhalve kan dit model als leidraad dienen voor het voorschrijven van antistollingsmedicatie aan patiënten met onderbeengips en na arthroscopie van de knie. Op deze manier zouden hoog-risicopatiënten selectief behandeld kunnen worden met (eventueel een hogere dosis) antistollingsmedicatie, terwijl laag-risicopatiënten niet blootgesteld worden aan de risico's en belasting van behandeling met antistollingsmedicatie.

Conclusie en implicaties

Patiënten met onderbeengips en na arthroscopie van de knie hebben een verhoogd risico op veneuze trombose. Ondanks dit hogere risico gaf routinematige behandeling met antistollingsmedicatie (laagmoleculairgewichtheparine) geen duidelijke vermindering van het optreden van het aantal veneuze trombose. Derhalve is het advies om niet routinematig tromboseprofylaxe met profylactische dosering antistollingsmedicatie toe te passen bij deze patiëntengroepen. Desondanks ontwikkeld een aanzienlijk deel van deze patiënten een veneuze trombose. Eventuele behandeling met een hogere dosis antistollingsmedicatie of langere behandeling lijkt niet zinvol voor de hele populatie omdat hiermee zeer waarschijnlijk ook het risico op bloedingen omhoog zal gaan. Het veneuze trombose risico varieert per patiënt op basis van de aanwezigheid van andere verworven of genetische risicofactoren. De predictiemodellen die opgesteld zijn voor het voorspellen van het optreden van veneuze trombose na arthroscopie van de knie en bij behandeling met onderbeengips kunnen gebruikt worden om hoog risicopatiënten te identificeren. Deze modellen zullen getest moeten worden in nader onderzoek om te kijken of het selectief behandelen (eventueel met een hogere dosis antistolling) inderdaad een veilige manier is om veneuze trombose te voorkomen, zonder dat hierbij het risico van behandeling (met name bloedingen) omhoog gaat. We zullen van een populatie brede aanpak richting geïndividualiseerde behandelstrategieën moeten gaan om zo tot de beste behandeling voor iedere patiënt te kunnen komen en de orthopaedische patiënten in beweging kunnen houden.

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Curriculum vitae

Raymond Alexander van Adrichem was born on the 6th of January in Delft, the Netherlands. He graduated from the 'ISW' in 's-Gravenzande in 1997, after which he started to study medicine at the Leiden University Medical Center. During his medical study he worked as a teaching assistant at the department of Anatomy and as an assistant in orthopedic surgery instructional courses for Kyphon International/Medtronic in Leiden and Brussels.

After obtaining his medical degree in 2010 he started to work as a junior doctor at the department of Orthopedic Surgery in the Medical Center Haaglanden (nowadays Haaglanden Medical Center), the Hague (Dr. E.R.A van Arkel). From 2011 onwards he worked as a PhD-Student at the department of Clinical Epidemiology (Prof. Dr. S.C. Cannegieter) and Orthopedic Surgery (Prof. Dr. R.G.H.H. Nelissen) on the subject of prevention of venous thromboembolism in orthopedic surgery. He coordinated the Pot-(K)Cast trials, two large multicenter randomized controlled trials on the prevention of venous thromboembolism in patients with cast immobilization of the lower leg and after arthroscopy of the knee. Results from this study and others studies described in this thesis were published in highly ranked peer reviewed international journals and presented at national and international conferences. For several studies he received research awards and he was an invited speaker at national conferences. In addition, during his PhD research he completed the training program to become a clinical epidemiologist.

In 2015 he started with his residency to become an orthopedic surgeon. He performed his general surgery residency in the Alrijne hospital in Leiderdorp (Dr. A.M. Zeillemaker). In 2017 he continued at the department of Orthopedic Surgery in the Haga hospital in the Hague (Dr. R.L.M Deijkers). In 2018 and 2019 he worked as a resident orthopedic surgery in the LUMC (Prof. Dr. R.G.H.H. Nelissen). From 2020 onwards he works as a resident orthopedic surgery once again in the Haga hospital in the Hague and the Reinier Haga Orthopedic Centre in Zoetermeer (J.C.T. van der Lugt). He will finish his residency to become an orthopedic surgeon in 2022. Raymond is the proud father of Noor, with a second child coming up and lives happily with Kim in Leiden.