Thrombosis prophylaxis after knee arthroscopy or during lower leg cast immobilization : determining the balance between benefits and risks

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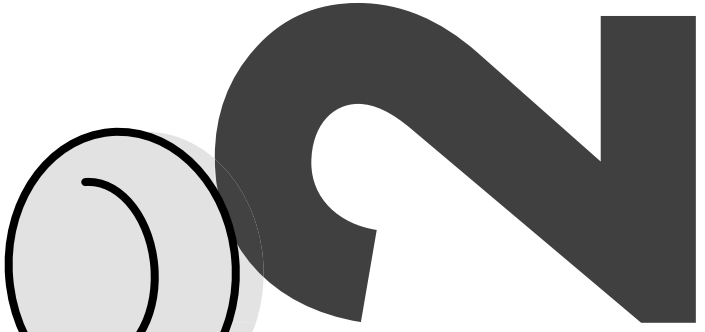
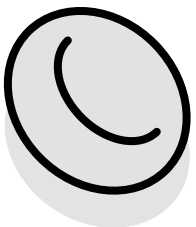


CHAPTER

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



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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.

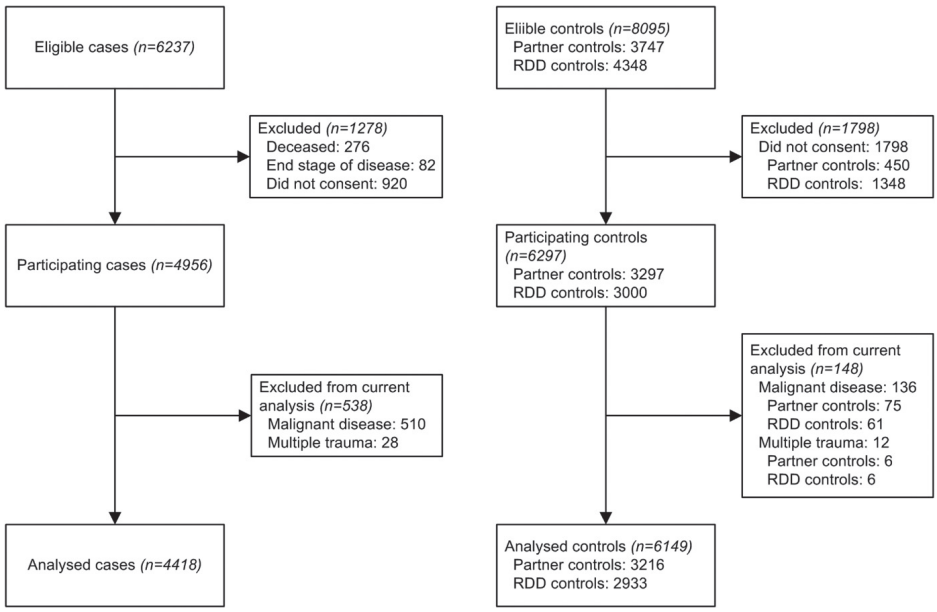

Figure 1. *Flow chart of eligible and analyzed cases and controls.*
Description: Flow chart of eligible and analyzed cases and controls. RDD: Random digit dialing controls.

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

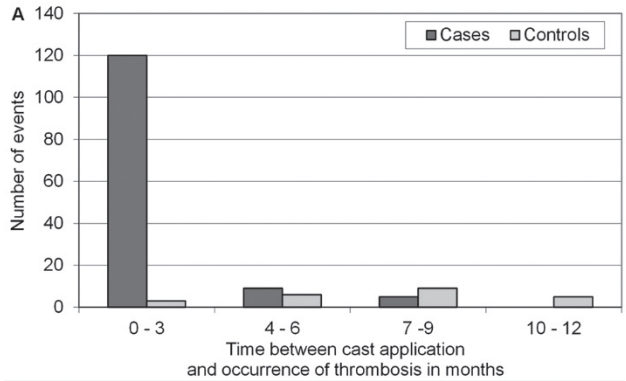

Figure 2a. *Frequency of the occurrence of events in months within one year after below-knee cast application.*

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).

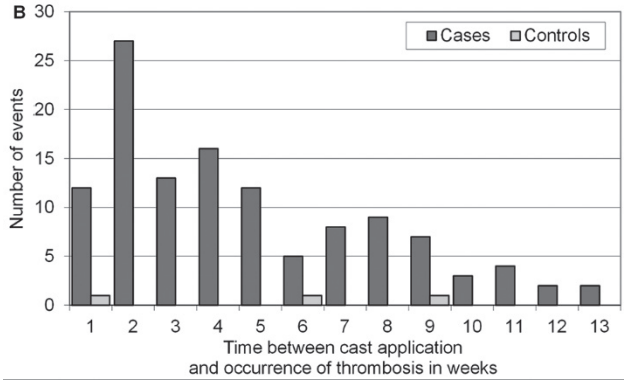

Figure 2b. *Frequency of the occurrence of events within the first 13 weeks after below-knee cast application.*

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.

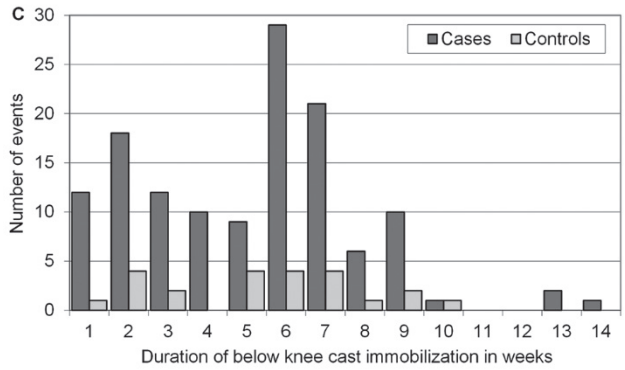

Figure 2c. *Frequency of the occurrence of events for different durations of below-knee cast immobilization.*

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.*