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Venous thrombosis following lower-leg cast immobilization and knee arthroscopy: From a population-based approach to individualized therapy

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High risk of recurrent venous thrombosis in patients with lower-leg cast immobilization

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ABSTRACT

Background Patients with lower-leg cast immobilization have a substantially increased risk to develop a first venous thrombosis (VT) while the risk in patients with a history of VT is as yet unknown.

Aims To estimate the risk of a recurrent thrombotic event after lower-leg cast immobilization in patients with a history of VT.

Methods This study is a case-control study nested within a cohort of 4597 patients with a first VT who were followed over time for recurrence from 1999-2010 (MEGA follow-up study). Participants completed a questionnaire on risk factors for recurrent thrombosis, including plaster cast in the first 3 months before a recurrence (cases) or a random 3 month-period during follow-up for participants without recurrence (controls). In total, 2723/4597 (59%) participants returned the questionnaire. Odds ratios (OR), adjusted for age and sex were calculated to compare risks of recurrence between subjects with and without cast.

Results 2525/2723 participants (93%) filled out information on plaster cast immobilization. Twenty (1.0%) controls and ten (2.2%) cases reported to have had lower-leg casting in the three months before control or recurrence date, for an adjusted OR of 2.4 (95% Confidence Interval 1.1-5.3). Thereafter we cross checked the data with these patients' medical records. Plaster cast application within 3-months was verified in seven (0.3%) controls versus six (1.3%) cases leading to an adjusted OR of 4.5 (95% CI: 1.5-14.0), for a corresponding cumulative incidence or 3.2%.

Conclusions Lower-leg cast immobilization increases the risk of recurrent VT in the 3 months after its application in patients with a history of VT.

INTRODUCTION

Patients who are treated with lower-leg cast immobilization have a substantially increased risk (about 1-2%) to develop Venous Thrombosis (VT) (i.e. deep vein thrombosis [DVT] and pulmonary embolism [PE]).[1, 2] However, the risk to develop a recurrent VT following cast immobilization in patients with a history of VT is as yet unknown. Knowledge on this risk can further support clinical policy regarding thromboprophylaxis treatment in these patients. Unfortunately, almost all large trials on this topic excluded patients with a history of VT so that precise risk estimations cannot be made.[3-8]

To date, multiple studies have focused on the prediction of a recurrent event (for both unprovoked and provoked recurrent events) by using risk factors that are present during the first venous thrombotic event. Yet, these risk assessment models lack discriminative ability which is not surprising, as prediction of a provoked recurrent event is challenging.[9] For optimal prophylactic strategies, identifying the risk for recurrence around periods with an increased thrombosis potential (such as cast immobilization) is crucial for the prevention of a provoked recurrent event. In this study we aimed to estimate the risk of a recurrent VT shortly after lower-leg cast immobilization in patients with a history of VT.

METHODS

Study population

We used data from the Multiple Environmental and Genetic Assessment follow up study (MEGA-follow up study). Details of this study have been published previously.[10] In short, the MEGA study is a population-based case-control study into the aetiology of VT. 4.956 consecutive patients with a first DVT, PE or both were recruited from six anticoagulation clinics in the Netherlands between 1999 and 2004. The diagnosis was confirmed by (Doppler) ultrasonography, ventilation-perfusion scan, angiography or spiral CT-scan. Control subjects were either partners of cases or recruited via random digit dialling.[11] Thereafter, the MEGA follow-up study was performed, details were also published previously.[12] 4731 cases who participated in the MEGA case-control study agreed to participate in the follow up study. Patients were followed over time to determine incidence rates for recurrent VT from 1999 until 2010. Between 2007 and 2009 the vital status of all patients was acquired from the central Dutch Population Register and the cause of death was obtained from the national register of death certificates. Recurrences were classified into certain and uncertain recurrences (information was obtained from questionnaires, hospital discharge letters, anticoagulation clinics and death certificates). For this analysis only certain recurrences were used. In addition, the MEGA follow-up database was linked to The Dutch Foundation for Pharmaceutical Statistics database, that provides information on all medical prescriptions from 95% of all public pharmacies in the Netherlands.[13] By doing so, medication usage (during the study period) for >90% of all participants in the study was objectively obtained. The MEGA follow-up study was approved by the Medical Ethics Committee of the Leiden University Medical Center and all participants gave informed consent.

Data collection

Participants were asked to complete a questionnaire on putative risk factors for recurrent VT by asking information on the period previous to the recurrent event or a random control period for participants who did not develop a recurrence. Plaster cast application of the lower extremities was identified with the question "Did you have plaster cast within 3 months previous to your second VT?". Plaster cast location and date were also recorded. For those patients who did not develop a recurrence the same question was asked, only the reference date was a 3-month period before a random control date.

Statistical analysis

We performed a nested case-control study within the MEGA follow-up study cohort. Patients with an uncertain recurrence diagnosis were excluded. Cases (patients with a recurrent VT) and controls (those without a recurrent VT) were identified at the end

of follow up. Finally, cases and controls who did not complete the questionnaire, or in whom information on plaster cast immobilization was missing were also excluded from the analysis. (*Figure 1*).

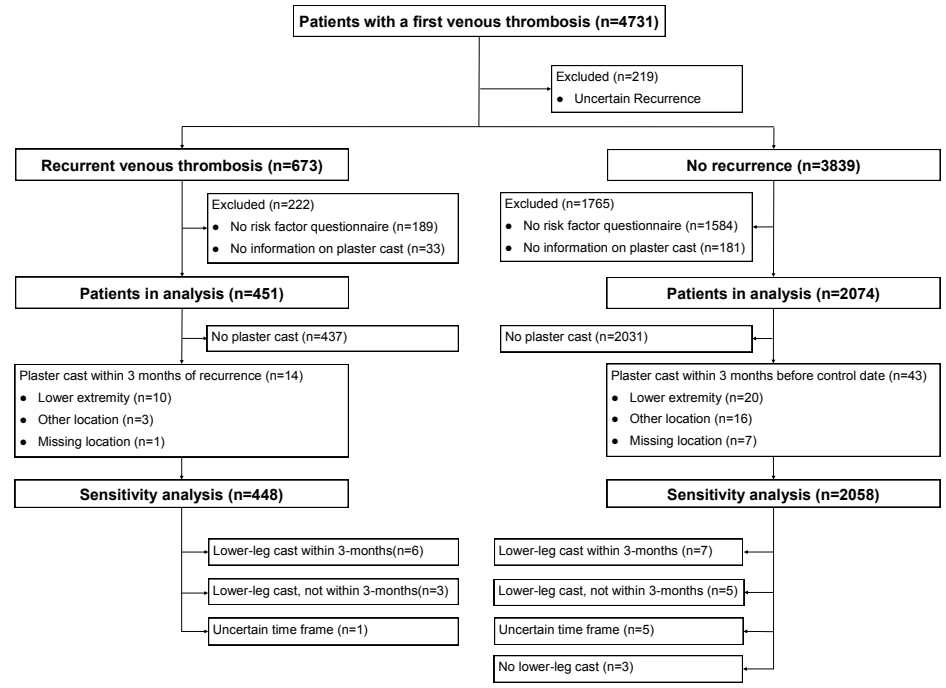

Figure 1: Study flow chart and number of patients included in the analyses.

To compare the risk of recurrence between subjects with and without plaster cast (all locations) we estimated the Relative Risk (RR) by calculating the Odds Ratio (OR) with the 95% Confidence Interval (95%CI). In addition, an OR (OR_{adj}) adjusted for age and sex was calculated using binary logistic regression. First, we calculated the OR for the development of recurrent VT for all types of cast immobilization. Subsequently, individuals with plaster cast of another location than lower-leg cast, or missing location, were excluded. Then we calculated the OR for recurrence for subjects with and without lower-leg cast. Finally, after verifying plaster date and recurrence date in the patients' records (to check the 3-month window of cast exposure previous to a patients VT or control date), we calculated the risk of recurrence between subjects with and without certain lower-leg cast (sensitivity analysis, *Figure 1*).

RESULTS AND DISCUSSION

4731 cases from the MEGA study agreed to participate in the MEGA follow-up study. After exclusion of participants with an uncertain recurrence (n=219), 673/4731 (14%) cases with a certain recurrence and 3839/4731 (81%) control subjects without recurrence were identified. 451 cases were included in the analysis after exclusion of cases with missing information on plaster cast (n=33) and cases who did not fill out the questionnaire on risk factors (n=189). Likewise, in 181 controls, information on plaster cast was missing and 1584 controls did not complete the questionnaire on risk factors, leaving 2074 controls for the analysis (*Figure 1*). The mean age of the study cohort was 47.7 years and 44.2% was male.

Of all cases, 14/451 subjects had any plaster cast within 3 months prior to their recurrent VT (10 lower-extremity, 3 other location, 1 missing location) and so did 43/2074 controls (20 lower extremity, 16 other location and 7 missing location, 3 months prior to the control date), for an OR of 1.5 (95%CI 0.8 - 2.8) (*Table 1*).

Table 1: The risk of recurrent venous thrombosis in individuals with lower-leg cast immobilization.

	Cases with cast	**Controls with cast**	**OR (95% CI)**	***OR_{adj} (95% CI)**
Original analysis				
All cast	14	43	1.5 (0.8-2.8)	1.6 (0.8-2.9)
Lower-leg cast	10	20	2.3 (1.1-5.0)	2.4 (1.1-5.3)
Sensitivity analysis†				
Certain lower-leg cast	6	7	4.0 (1.3-11.9)	4.5 (1.5-14.0)

*OR_{adj} denotes adjusted Odds Ratio for age and sex, CI denotes Confidence Interval
† Confirmed lower-leg cast within 3-month window from a patients' medical record

Subsequently, 4 cases and 23 controls were excluded because of a plaster cast location other than the lower extremities (i.e. arm, hand, finger and spine), or missing location, leaving subjects with or without plaster cast of the lower extremities only (10 cases and 20 controls with lower-leg cast). These patients had a 2.3-fold increased risk for developing a recurrent VT (95% CI 1.1 – 5.0), which hardly changed after adjustment for age and sex (OR_{adj} 2.4 (95%CI 1.1 – 5.3)) (*Table 1*). As these risks were self-reported we cross-checked the recurrence date and plaster date in the patients' medical records or discharge letter. By doing so, we were able to confirm cast of the lower-leg within 3 months prior to the recurrent VT/control period in 6/448 cases and 7/2058 controls. In most other patients the plaster cast date did not match the 3-month window before the recurrence

date. Therefore, these patients did have plaster cast, but not within the 3-month window. This further refinement resulted in a 4.0-fold increased risk for recurrent VT (95%CI 1.3 – 11.9) and adjusted for age and sex OR_{adj} 4.5 (95%CI 1.5 – 14.0) (*Table 1*). A corresponding cumulative incidence at 3 months of 3.2% can be derived from these numbers (28.1 recurrent VT cases per 1000 individuals per year (baseline) times 4.5 = 126.4/1000/year, thus 31.6/1000 (3.2%) recurrent events within 3 months following lower-leg cast immobilisation. By reviewing discharge letters and medical records it was showed that most cases and controls with a recurrence did not have a prescription of anticoagulation medication during plaster cast immobilization. However, this may be explained due to the fact that these prescriptions probably were issued at the hospital pharmacies (which were not linked to this database). Therefore, we cannot state for certain that these patients received prophylactic therapy.

Our results might be limited by misclassification of the plaster cast date i.e. unintendedly misclassifying a case or a control as having [or not having] a lower-leg cast within 3-months. Therefore, to verify our results, we performed a sensitivity analysis which showed that mainly controls had been misclassified (they did have a lower-leg cast, but not within 3-months). This refinement led to a 4.5-fold increased risk for VT. In addition, controls were sampled at the end of follow up and not matched on follow-up duration with cases. This approach may have led to an underestimation of the actual risk if controls, that were lost to follow up, for example died because of a lung embolism due to plaster cast immobilization although this is unlikely. Finally, it is unknown whether all patients received thromboprophylaxis during cast-immobilization. However, according to a recent survey study conducted in the Netherlands, thromboprophylactic therapy was always prescribed for patients with plaster cast immobilization of the lower-leg in 79% and 63% of patients by trauma surgeons and orthopaedic surgeons respectively, and if any risk factors were present (such as VT in patients history) in an additional 15% and 33% of patients, by trauma and orthopaedic surgeons respectively.[14] Therefore it is likely that almost all patients received thromboprophylactic therapy during immobilization.

Recently, van Adrichem et al reported that patients with cast immobilization of the lower-leg have a 32-fold risk for developing a first VT within 3 months.[1] The lower risk that we found (between 2.4 and 4.5-fold increased) for recurrent VT after plaster cast application might partly be explained by thromboprophylactic therapy, as patients with a history of VT have a high risk of developing a recurrence and therefore clinicians may be more willing to prescribe thromboprophylactic therapy than for a first event. Another explanation for this lower risk is the high baseline risk for recurrent VT as compared with the baseline risk for a first VT, also known as the "recurrence paradox".[15] Suppose that in absolute terms, the baseline risk for a first VT is 1 per 1000 individuals per year, thus 0.25 per 3-months[16].

Considering a relative risk of 32, this leads to an absolute risk for VT following lower-leg cast of about 8 per 1000 individuals within 3-months (thus 7.75 extra cases). Now, consider a population at risk for recurrent VT at an incidence rate of 30 per 1000 individuals per years, thus 7.5 per 3-months)[17]. The extra VT risk due to lower-leg cast immobilization would lead to 7.5 plus 7.75=15.25 cases per 1000 individuals within 3-month, thus a relative risk of 2.1 (15.25 divided by 7.5). Consequently, the relative risk for recurrence is lower compared with the risk of a first VT after cast immobilization.

For patients with a history of VT, most guidelines advise to asses VT and bleeding risk in circumstances of an increased risk (e.g. surgery, hospitalization etc.). Patients with a personal history of VT are considered to be at high risk for the development of a recurrence during these situations. Therefore all guidelines advise to give thromboprophylactic therapy in these situations, for example during cast immobilization.[18, 19] In our study, patients with a history of VT and casting of the lower-leg had a 4.5-fold increased risk, corresponding cumulative incidence at 3 months of 3.2%. Based on this high risk we carefully suggest that in patients with a history of VT and subsequent lower-leg cast immobilization, a prophylactic dosage might not be sufficient and therapeutic dosages should be considered on an individual patient basis. However, with the risk of bias and unknown information on prophylactic therapy in our study taken into account, our advice should be interpreted with caution. Also, an individual's bleeding risk has to be determined before such interventions can be applied. At any rate, antithrombotic medication is strongly advised for patients with cast immobilization of the lower-leg and a history of VT.

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