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

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

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ABSTRACT

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. Using a population-based case-control study into the aetiology 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. 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 haemorheological 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.

INTRODUCTION

In general, orthopaedic 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 orthopaedic 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 dialling 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 orthopaedic 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 hemorheologic and other markers can be found in *Supplement 1*. 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 orthopaedic 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. *Supplement 2* provides detailed information on missing data for risk factors incorporated in the prediction model.

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*) (*Figure 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*.

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 aetiology 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.

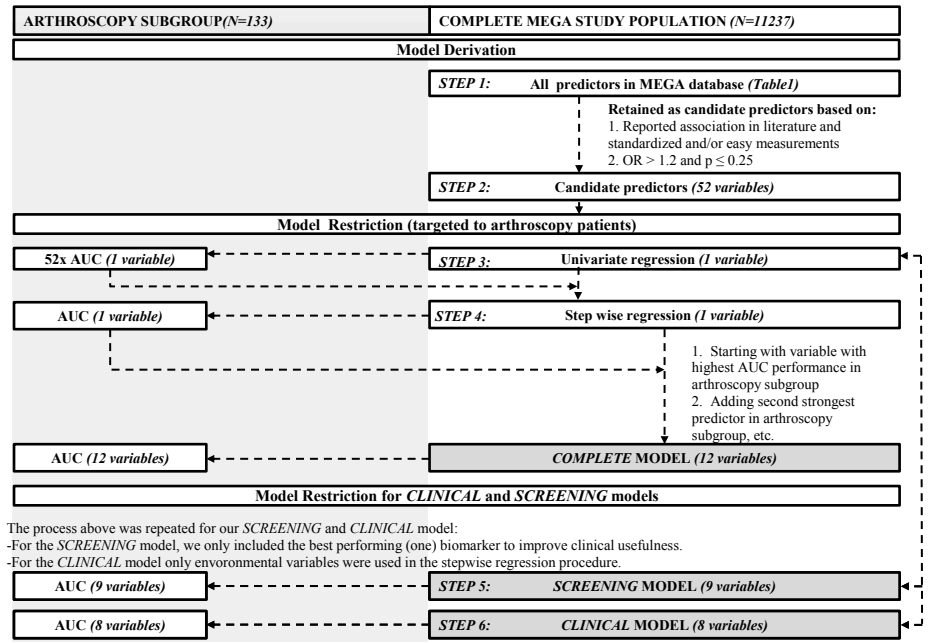

Figure 1: Flow-chart of the derivation process for development of the *L-TRiP(ascopy)* score.

RESULTS

Study population

4 943 cases and 6 294 controls were maintained in the analyses after exclusion of 13 participants who underwent multiple orthopaedic 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.

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

Table 1: Continued.

Environmental predictor variables	
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
Hemorheologic and coagulation predictor variables	
Fibrinogen activity	Percentage/number granulocytes
Factor VIII activity	Red Blood Cell Count (RBCC)
Von Willebrand Factor (vWF) (%)	Haemoglobin level
Factor II activity	Mean Cell Volume (MCV)
Factor VII activity	Mean Cell Haemoglobin (MCH)
Factor X antigen level	Mean Cell Haemoglobin Concentration (MCHC)
Protein C activity	Red cell Distribution With (RDW)
Factor XI activity	Antithrombin activity
Haematocrit	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	

Complete model

Twelve predictor variables (8 environmental risk factors, 3 hemorheologic 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 2: AUC values of the *Complete, Screening, Clinical model* and *L-TRiP(ascopy) score* in the MEGA and VTE study.

	MEGA study			**Internal validation**			**External validation: VTE study**		
Model	**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

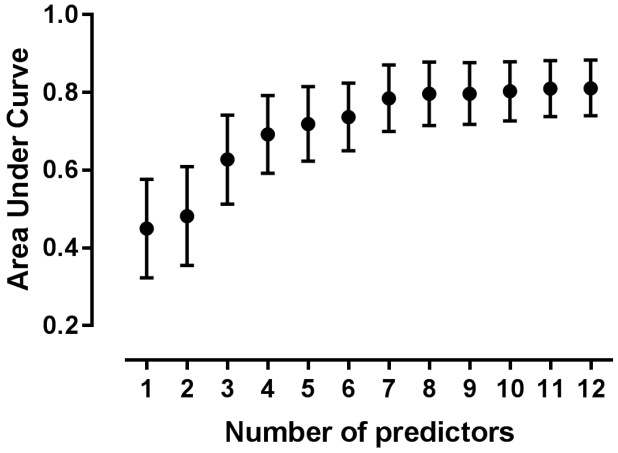

Figure 2: AUC values of the *Complete* model for step-wise addition of the following predictors: age, sex, von Willebrand Factor activity, family history of VT, Factor V Leiden mutation, being bedridden within the past 3 months, current use of oral contraceptives, (type) of knee arthroscopy, Factor VIII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

Table 4: L-TRiP(ascopy) score performance

Cutpoint	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%

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.

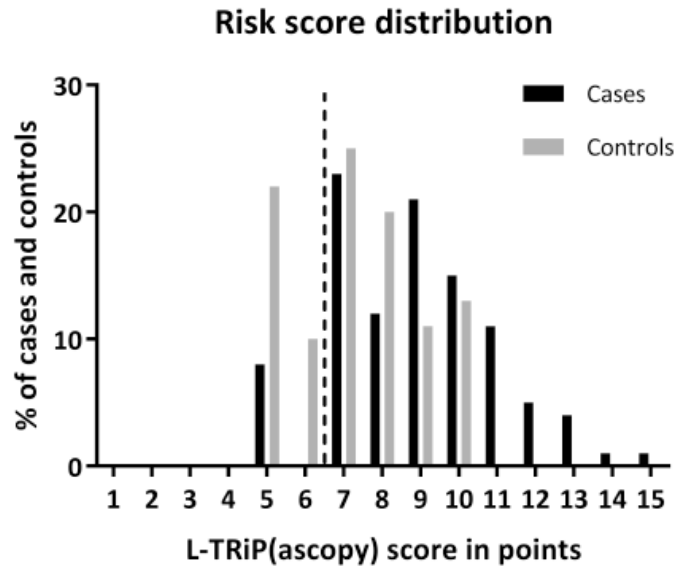

Figure 3: Risk score distribution among cases and controls for the *L-TRiP(ascopy)score*. Dashed black lines represent Cut-off values that correspond to a test sensitivity of 75%.

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 VTE, for instance the Caprini score[23]. According to this score, patients who undergo arthroscopic surgery score 2 points, indicating a moderate risk for VTE. 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 orthopaedic 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 VTE prevention following knee arthroscopy[12], the effect of prophylaxis on VTE 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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